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THE EFFECT OF ORAL ADMINISTRATION OF "AMINO ACIDS" ON THE HYPOPROTEINEMIA RESULTING FROM BLEEDING PEPTIC ULCER[1]

PRELIMINARY REPORT

JEROME S. LEVY, MAJOR, M.C.[2]

INTRODUCTION

Re-evaluation of treatment of the bleeding peptic ulcer was initiated by Meulengracht (1) by his study indicating a lowered mortality rate resulted from an early feeding plan. Following his publication, there have been numerous reports of mortality statistics which range from zero to 50%. An analysis of the reported data reveals that the discrepancies are more apparent than real. In some instances, the lower figures are attributed mainly to the effects of the treatment. Disregard of other factors which must be considered in the proper evaluation of this important subject has been conspicuous. The purpose of this paper is threefold: 1) To analyze some of the most important physiological reactions to bleeding; 2) To evaluate their relation to treatment and prognosis in the case of the bleeding peptic ulcer; and 3) To observe the effects of the use of a casein hydrolysate in these cases.

FACTORS INFLUENCING MORTALITY

The main factors influencing mortality from a bleeding point in the upper gastro-intestinal tract definitely are the age of the patient, the severity of the hemorrhage, and the presence of complicating diseases, although the greatest probable factor is the kind of lesion itself; i.e., the presence or absence of a large, open, "pipestem" artery.

Age

The influence of age is well shown by the following reports. Blackford and Allen (2) have reviewed the death certificates recorded in the Bureau of Vital Statistics, Seattle, Washington. Between 1935–1941, 151 deaths from bleeding peptic ulcer had been recorded. They found that 95% of deaths were in the

[1] From the Department of Medicine, University of Arkansas School of Medicine and from the Gastro-Intestinal Sub-Section, Bushnell General Hospital, Brigham City, Utah.
[2] Associate Professor of Medicine, University of Arkansas School of Medicine, Little Rock, Arkansas; on leave of absence during military service.

case of persons past the age of 45 years. Of equal interest was the fact that 77% of deaths followed the first hemorrhage. Meyer, Sorter, and Necheles (3) reviewed the records of 154 cases of hemorrhage from peptic ulcer in patients admitted to Michael Reese Hospital over a ten year period. Eight deaths (7.2%) occurred in 111 patients who had been treated medically. All of the deaths were in patients over the age of 45 years.

In this group of 111 cases, 71 were over 45 years of age, resulting in a mortality rate of 11.3% in this age group. In a group of 27 cases treated surgically, 6 (22.2%) died. Of these, three were above 45 years of age, the other three were less than 45. The deaths that occurred in those less than 45, all of whom had been subjected to surgery, constituted 2.1% of the total admissions for bleeding. Rafsky and Weingarten (4) studied 408 cases observed in two hospitals from 1927 to 1941. These patients were treated with different methods of medical therapy. When analyzed on the basis of age groups, there was no significant difference in the number of deaths when the different methods of treatment were considered. Among 270 cases below the age of 50, there were 13 (4.8%) deaths. In 138 cases over age of 50 there were 23 (16.6%) deaths. In only 18 (or 4.4% of all cases) was hemorrhage the sole cause of death. The other deaths were due to complicating diseases. The authors, also, noted the high incidence (64%) of deaths resulting from the first hemorrhage. These three statistical studies when reviewed with reference to age clearly reveal the importance of this factor on the mortality rate from hemorrhage.

Extent of hemorrhage

The second factor which influences the recovery from hemorrhage is the degree of bleeding. There has been no uniformity in the determination of the grade of hemorrhage. It is difficult to compare accurately clinical data recorded as slight, moderate or severe hemorrhage. A classification should be established in order that statistical studies may be more correctly compared. Rafsky and Weingarten (4) have proposed and used a fairly satisfactory classification for grading the severity of hemorrhage (table 1). The red cell counts and hemoglobin estimations were used for the basis of grading. They consider a red cell count of 4,000,000 or more with hemoglobin of 12.0 grams or more a grade one hemorrhage. A red blood cell range of 3,000,000 to 3,990,000 with a hemoglobin range of 9.0 grams to 11.8 grams constitutes grade two. A range of 2,250,000 to 2,990,000 red blood cells with 6.8 grams to 8.8 grams hemoglobin indicates a grade three and a count of less than 2,250,000 with hemoglobin less than 6.8 grams is considered grade four. If there occurs a disagreement between the red cell count and the hemoglobin, the general condition of the patient is evaluated in deciding whether or not the lower figure

should be considered as an index. It is interesting to note that in their 408 cases they report no deaths due to hemorrhage of grade one and two, although 8 died of complicating diseases, a mortality of 7.2%. In the group with hemorrhage grade 3, seven died, although only four were from bleeding per se. There were 21 deaths in the group with grade 4, but only 14 from bleeding alone.

Hypoproteinemia

This classification does not include one of the most important effects of massive hemorrhage: that is, the resultant hypoproteinemia. I believe a consideration of the serum or plasma protein should be added to the criteria. This will tend to give a much clearer conception of the severity of the hemorrhage and will also direct attention to one of the gravest effects of the blood loss. A determination of the serum or plasma protein is easily done with either the falling drop method (5) or the copper sulphate method (6). With either method, the blood protein level can be determined within a few minutes.

TABLE 1*

Classification of Hemorrhage

GRADE	RBC IN MILLIONS	Hb
		grams
1	4.0 plus	12.0+
2	3.9–3.0	9.0–11.8
3	2.9–2.25	6.8– 8.8
4	less than 2.25	less than 6.8

* Rafsky and Weingarten (4).

The importance of the hypoproteinemia which results from massive gastroduodenal bleeding has received only scant attention. There have been, on the other hand, numerous investigations of the significance of lowered plasma protein in surgical conditions. The effect of hypoproteinemia on wound healing, in burns, in obstructions, post-operative states, and so on, has become well known. Elman (7) has shown that it required days after experimental hemorrhage to restore to normal the plasma protein of the hypoproteinemic dog. This also has been observed in man as will be shown.

The disturbance in the body metabolism generally and in the repair of damaged tissue in particular are important factors in any disease process. In a bleeding peptic ulcer this is as important as in any other pathological condition. With the diminution of the plasma protein levels, there is a definite delay in wound healing. Whipple (8) and Rhoads, Fliegelman, and Panzer (9) have demonstrated a significant lag in wound repair in animals in whom the plasma proteins have been reduced by feeding and plasmophoresis experi-

ments. The investigations by Rhoads et al. (9) have demonstrated a change in osmotic pressure of the blood and intercellular fluids which interferes with the utilization of whatever protein is available, even though the percentage is decreased. It is a safe assumption to make that this is as important in the repair of a peptic ulcer as it is in the repair of a surgical wound.

Mecray, Barden and Ravdin (1) have studied the effects of hypoproteinemia in animals following a gastro-enterostomy. These authors demonstrated that hypoproteinemia produces a delay in gastric emptying, even in the presence of increased peristalsis in these animals. This is explained by a physiologic obstruction due to edema of the gastric wall surrounding the stoma. This edema disappears when the blood protein levels approach normal. In the case of an acute ulcer in the stomach or duodenum, especially if near the pylorus, it is only logical to suspect that a similar edema exists with resultant interference with emptying of the stomach when a massive hemorrhage has lowered the plasma protein. Other studies (11) have shown that there is an interference with absorption from the small intestine in the presence of hypo-

TABLE 2

GRADE	PLASMA PROTEIN
1	6.50 gms. or above
2	6.49 to 6.00
3	5.99 to 5.5
4	5.49 or below

proteinemia. It follows, therefore, that in such an alteration of the body physiology, hypoproteinemia following gastric hemorrhage should receive more careful attention. *It is then particularly suggested that plasma protein levels should be added to any criteria for the purpose of grading the degree of hemorrhage.*

A method for grading the degree of hemorrhage on the basis of blood protein values is suggested in table 2.

The criteria for establishing the grade or severity of the hemorrhage would consist of the red blood cell count, the hemoglobin, and the blood protein. Either the plasma protein or the serum protein is acceptable as the difference between them is of no significance. Agreement between two of the three criteria would be accepted as the basis for grading the individual case. Table 3 shows the levels of the red blood cells, hemoglobin, and plasma protein in 17 cases following massive gastro-duodenal hemorrhage.

Should there still be a doubt, the clinical condition of the patient would influence the borderline interpretation.

Clinical condition

The patients were graded also according to the apparent clinical condition and this grade was compared with that based on the laboratory data as above described. In cases 2, 4, 11, 15 and 17, the clinical grade was less than the laboratory grade. In case 5 the patient was in acute shock on admission and remained so for nearly twelve hours in spite of all efforts to combat it, yet the

TABLE 3

Chart of clinical data in cases of gastro-duodenal bleeding

NO.	SEX	AGE	PREVIOUS HEMORRHAGE	DURATION OF BLEEDING	GRADE OF HEMORRHAGE*		Hb GM. OR %	RBC†	NPN	PLASMA PROTEIN	NUTRITION
					C	L					
										gms.	
1	M	17	0	4 days	4	4	22%	1.29		3.8	Good
2	M	20	0	4 days	3	4	4.75	1.35	54	4.83	Good
3	M	59	0	Few hrs.	2	2	8.5	3.04	100	5.93	Good
4‡	M	68	0	slight for 2 weeks	2	3	7.0	2.55	51	6.75	Good
5	M	44	1	24 hrs.	4	3	9.3	2.82	75	4.9	Excellent
6	M	34	0	20 hrs.	2	2	11.2	3.8	45	6.5	Good
7	M	73	0	2 hrs.	4	4	32%	2.05		3.85	Fair
8§	M	62	1	4 hrs.	4	4	5	1.99	74	4.94 5.90	Fair
9‖	M	31	0	7–10 days	4	4	5.25	1.54	50	4.69	Good
10	F	70	0	2 days?	3	3	7.0	2.45	83	4.97	Fair
11	M	33	0	4 days	3	4	5.75	1.35	48	4.08	Good
12*	M	65	0	8 days	3–4	3	7.75	2.5	50	4.49	Poor
13	M	45	0	2 days	4	4	30%	1.49	108	4.42	Good
14	M	60	1	1 day	4	4	3	1.36	151	5.14	Fair
15	M	41	0	2–3 days	3	4	35%	1.74	67	5.7	Fair
16	M	63		2–3 weeks	4	4	2.5	1.44	50	6.0	Poor
17	M	34	0	2 days	3	4	6.6	1.86	92	5.2	Good

* C—graded according to apparent clinical condition; L—graded on basis of laboratory data.
† RBC expressed in millions.
‡ Carcinoma of stomach.
§ Cirrhosis of liver; duodenal ulcer.
‖ Esophageal varices. All others are cases of duodenal ulcer.

laboratory examinations indicated a less severe degree of hemorrhage. The degree of the shock may have affected the blood studies. This was the only instance in which the clinical grade was more severe than the laboratory grade (table 3). Considering the overall picture of these cases, a classification based on the determination of plasma protein red cell and hemoglobin levels and the apparent clinical condition of the patient has proved satisfactory and it is

suggested as a more sound and complete basis for analyzing the effects of the different forms of treatment of massive gastro-duodenal hemorrhage.

THE RATIONALE FOR THE USE OF "AMINO ACIDS" IN BLEEDING PEPTIC ULCER

The value of early feeding, in my opinion, lies in supplying the tissues with exogenous protein. However, the mechanical effect of motor and digestive activity with full feedings may be sufficient to start further bleeding. In my opinion, the Meulengracht plan of feeding is associated with recurrence of bleeding more frequently than is the case with restricted diets. An ideal plan would be the incorporation of all of the advantages of a full dietary intake of protein without any of its disadvantages. Theoretically, the use of food which is already digested such as amigen[3] fulfils this requisite. This mixture should be an excellent antacid because of the amphoteric character of the amino acids, should require little digestive activity, should supply nitrogen for bodily needs and calories for metabolism. Siler and Levy (12) demonstrated the excellent buffering action of such a mixture. The pH of the stomach contents was raised to above 3.5 for a significant period of time. Above a pH of 3.5 there is not any free acid present and peptic activity is minimal. Above a pH 4.0, which they produced experimentally, peptic activity is practically nil. There was no unfavorable effect from the mixture when placed in the stomach. Elman (13) and others have shown that a positive nitrogen balance can be maintained by giving only a solution of amino acids by vein or subcutaneously. Plasma protein levels can also be maintained. Robscheit-Robbins, Miller, and Whipple (14) have shown that the injected amino acids are utilized for protein regeneration and for hemoglobin formation. Thomas and Crider (11) have demonstrated the inhibition of gastric motility when the end products of protein digestion are placed in the upper small intestine. It would seem, therefore, that in a mixture of amino acids, we have the necessary agents for correcting hypoproteinemia as well as having an excellent buffer for gastric acidity. Sufficient calories must be supplied, however, along with the protein digest or the amino acids will be utilized for caloric requirements rather than for correcting protein deficiencies. On these theoretical, experimental and clinical bases, a solution of amigen was used in the treatment of a group of cases with bleeding from the upper gastro-intestinal tract.

OBSERVATIONS

Cases admitted to the Gastro-Intestinal Service of the University Hospital, University of Arkansas School of Medicine and to the Gastro-Intestinal Sub-

[3] Amigen is the enzymatic hydrolysate of a pure casein supplied by Mead-Johnson Co. for this study. It contains *all* of the essential amino acids.

Section of Bushnell General Hospital comprise those studied. On admission, blood was taken from each patient for the determination of the red blood cell count, hemoglobin, white cell count and differential, hematocrit, NPN and serum protein. These laboratory studies were made daily. Transfusions of 500 cc. of plasma or whole blood were given when indicated for shock, or when the hemoglobin and red cell count fell below 35% and two million, respectively. As soon as the bleeding stopped, which was usually within 24 hours from the time of admission, 10% amigen in 10% glucose was given orally. The mixture was given as a constant drip through a Levin tube or in amounts of 90.0 cc. every hour as a substitute for the alkali in the Sippy[4] regimen. The patient ordinarily received 100.0 grams of amigen per day but this amount was increased when the serum protein did not show a satisfactory response. A maximum of 300.0 grams have been given in one day. The taste of the solution, which is none too pleasant, is improved by the addition of 0.5% salt and vanilla extract. Recently a preparation of amigen[5] has been made with salt and flavoring, which is much more palatable.

CLINICAL FINDINGS

Seventeen cases of bleeding from the upper gastro-intestinal tract were studied. While the total number is small, the observations are of sufficient significance to warrant reporting in order to stimulate additional investigations.

There was one death in this small series of cases. This patient was explored several weeks following the hemorrhage. On the seventh post-operative day, the wound broke open and the patient went into shock from which he did not recover. He had an advanced cirrhosis of the liver. It is believed that the death was not due to the hemorrhage nor to the treatment for the hemorrhage. The corrected mortality rate in this group shows no deaths from hemorrhage per se. Eight cases were below the age of 45. One of these had a grade 2, one had a grade 3 and the remainder had a grade 4 hemorrhage. In the 11 cases over the age of 45, considering the severity of the hemorrhage, at least one death from hemorrhage alone should have been expected.

Six of the cases reported were not treated with the amigen solution and may be considered as controls. They ranged in age from 17 to 68. Their nutritional state was good and their response to routine therapy of fluids and rest was satisfactory. Two of these had grade two, two grade three, and two grade four hemorrhages. The lowest protein value was 3.8 grams which was observed in the youngest (aged 17) patient (table 3). An average of 19.5 days was required to restore the serum protein to normal in this group of six patients.

[4] The usual Sippy diet of hourly feedings of a milk and cream mixture was given. Beginning on the 6th day, the diet was increased gradually as is customary.

[5] Amigen flavored for oral use.

Eleven cases were given amigen. Both groups received the same diet and *except for the amigen,* received equivalent daily nitrogen intake. In this group, the lowest serum protein observed was 3.95 grams. The solution was well tolerated in all. The ages of the patients given amigen ranged from 31 yrs. to 74 yrs. Three were below the age of 40, two were between 40 and 45, and the others were all over the age of 60.

Case 10 (fig. 1) is that of a woman, age 70, of poor nutritional state, who entered the hospital after two days of bleeding. She had a grade three hemorrhage. She

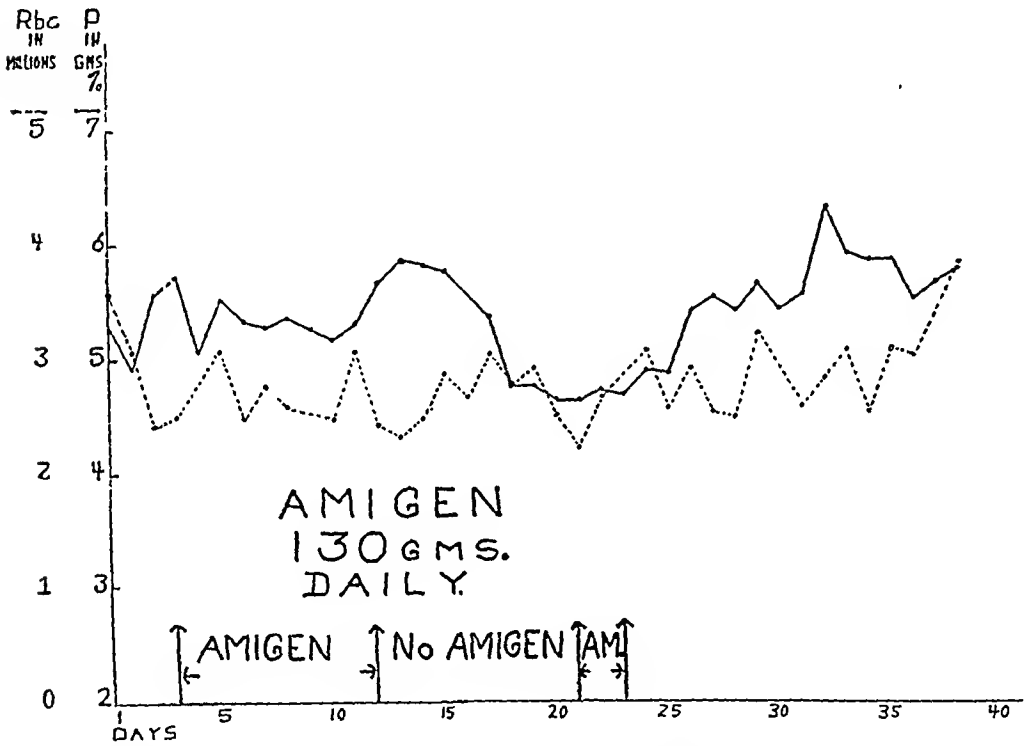

FIG. 1. CASE 10. DUODENAL ULCER

130 grams of amigen were given on the third through the twelfth days. Serum protein rose to 5.7 gm. followed by a fall to 4.5 gm. after the amigen was discontinued. Satisfactory rise again accompanied the use of amigen from 21st to 23rd days inclusive.

stopped bleeding promptly on admission to the hospital. Her serum protein was 4.97 grams. She was given 130 grams of amigen per day. There was a slow but steady increase of the serum protein. The amigen was discontinued on the 12th day. Even though the Sippy diet was being increased daily, the serum protein level fell during the next seven days. She was again given 130 grams of amigen for several days. The serum protein began to increase and reached 6.5 grams eleven days later. Case 11 (fig. 2) entered the hospital four days after his hemorrhage. His serum protein was 4.1 grams on admission. He was given 140 gms. of amigen the next day and 130 gms. daily thereafter for 10 days. The serum protein rose steadily to 6.0 gms. on the 12th day, when the amigen was discontinued. There was a moderately rapid fall

of the serum protein to 5.0 gms. within four days. Amigen in the amount of 130 gms. was again given each day for 3 days and there began a steady rise in the serum protein. When discharged three weeks later, the serum protein was 6.5 gms. (fig. 2). In these two cases, 130 gms. of amigen per day apparently produced a favorable rise in the serum protein, which promptly fell when the preparation was discontinued. *This occurred even though the diet was being increased daily.* A favorable response followed the readministration of amigen.

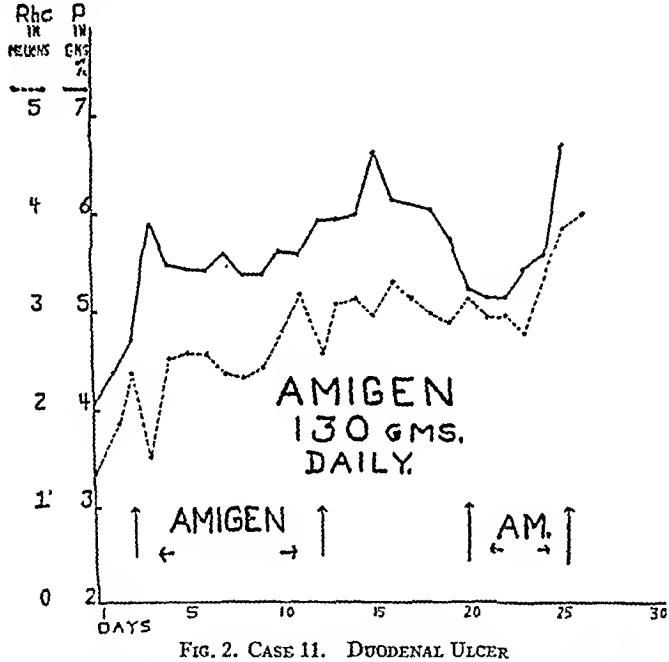

FIG. 2. CASE 11. DUODENAL ULCER

130 grams of amigen were given daily from the second through the twelfth days. Serum protein rose to 6.0 gm. but fell to 5.0 gm. after amigen was discontinued. Response of serum protein was prompt when amigen was given again on the twentieth through the twenty-fifth days.

Case 13 (fig. 3) had a severe (Grade 4) hemorrhage 2 days before hospitalization and continued to bleed intermittently during the first few days after his admission. The serum protein was 5.4 grams on the 8th day of hospitalization and he was started on 100 gms. of amigen daily. The serum protein continued to fall, reaching a low level of 4.42 gms. on 10th hospital day. He was then given 150 gms. of amigen daily. There was a prompt rise in the serum protein which continued and 15 days later it had resumed a normal level. The amigen was discontinued after the 22nd day of hospitalization (12 days after receiving 150 gms. per day). *Case 15* (fig. 4) also shows that larger amounts of amigen may be necessary to stimulate a more prompt and rapid increase of the serum protein. The smaller amounts of amigen maintained the serum protein between 5.14 gms. and 5.8 gms., while 200 gms. daily produced a steady and prompt rise to 6.6 gms. within 10 days. *Case 17* (fig. 5) shows the response to 100 gms. of amigen per day. This patient was in excellent health at the time of his

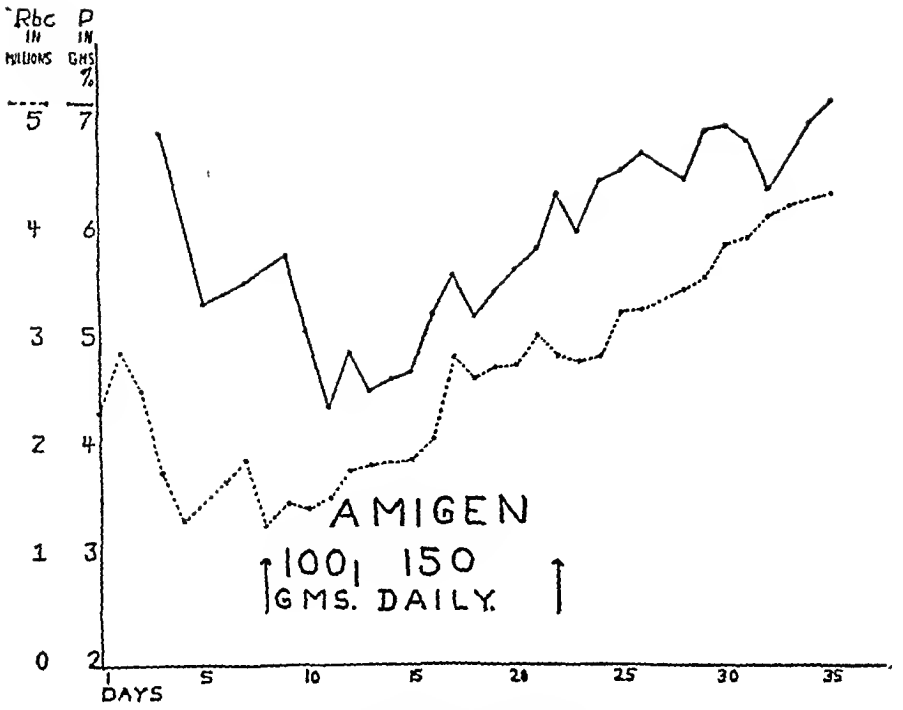

FIG. 3. CASE 13. GASTRIC ULCER

Steady fall in serum protein with 100 grams of amigen daily. Steady rise following increase of daily amount of amigen to 150 grams.

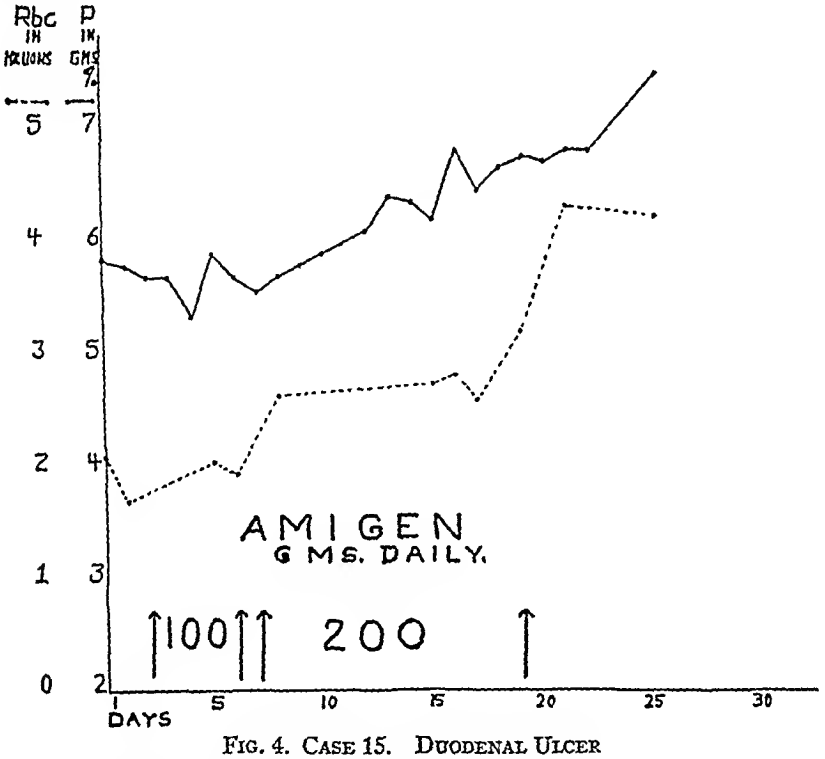

FIG. 4. CASE 15. DUODENAL ULCER

100 grams of amigen daily failed to maintain the serum protein. A prompt and steady rise resulted from giving 200 gm. per day.

hemorrhage and apparently did not need nitrogen for general nutritional needs. The response to the amino acids was prompt as shown by a rise from 5.1 gms. to 6.9 gms. in 13 days. The amigen was discontinued at this time and there was a gradual fall of the serum protein to 6.0 gms. on the 35th day. This fall occurred in spite of the progressive diet that he was taking.

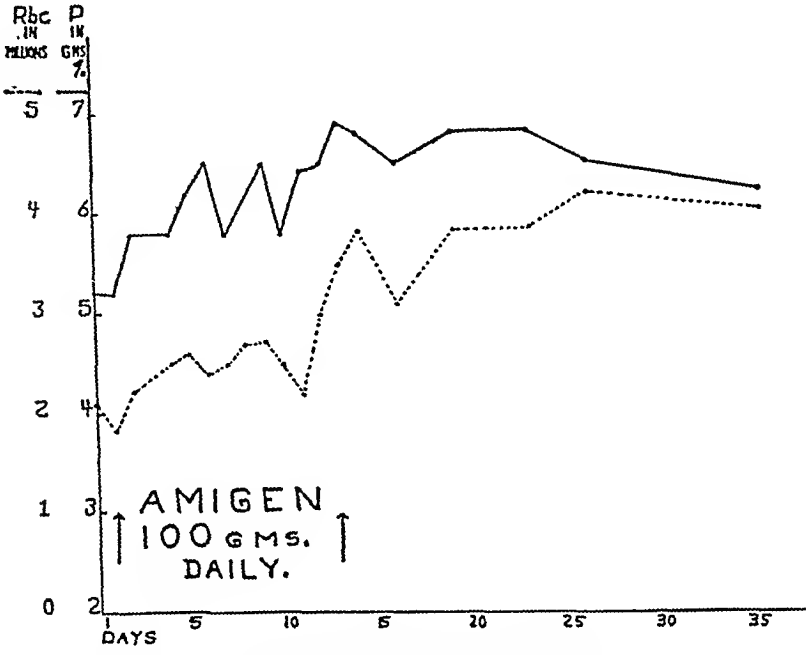

FIG. 5. CASE 17. DUODENAL ULCER

Response of serum protein to 100 grams of amigen daily in a patient in good state of nutrition. Serum protein of 6.9 grams in 14 days.

COMMENTS

A solution of a mixture of amino acids* have been given to eleven patients following hemorrhage from gastro-duodenal lesions. The solution was well tolerated. The materials for essential protein metabolism are provided for by the mixture of amino acids. Not only may they be utilized for repair or building of tissue protein and for restoration of serum protein, but they may be also utilized for meeting the caloric requirements when sufficient calories are not given. They may also aid in the production of hemoglobin. It was learned that it was necessary to give sufficient calories, mainly in the form of glucose, with the amigen. The protein loss in hemorrhage from peptic ulcer or carcinoma of the stomach is superimposed in many cases upon an already existing hypoproteinemia or a low normal serum protein. It is proposed,

* Amigen.

therefore, that the restoration of the serum protein should be recognized as a criterion for any satisfactory therapy.

The effect of the oral administration of amigen in this small series was very encouraging. In the six cases that did not receive amigen the serum protein returned to normal in an average of 19.5 days. In the eleven cases that *received amigen in sufficient quantities and with sufficient calories to meet the caloric requirements of the patient,* the serum protein showed a prompt and steady rise, reaching normal or near normal levels in from 10 to 12 days. The diet was the same in all cases; namely, a Sippy diet. The general nutritional condition of the patients given amigen was far below that of the six control cases. It would be suspected, therefore, that, under such circumstances, the serum protein levels would be more slowly restored, but, on the contrary, they returned to normal levels more rapidly.

The daily requirements of nitrogen in patients who have had a massive hemorrhage are not definitely known. One gram of protein per kilo of body weight is accepted as sufficient to meet the usual nitrogen requirements. One gram of antigen is equivalent to 0.8 gram of protein. In the cases of severe hypoproteinemia following massive gastro-duodenal hemorrhage it became evident that one gram per kilo was not sufficient. This was especially true when there was a co-existent malnutrition. Three to three and a half grams per kilo gave a more prompt and rapid increase of serum protein. It may be necessary in some cases to use a 20% solution in 10% glucose instead of a 10% solution in order to give sufficient amino acids.

The consistency of response of the amigen treated cases over the controls suggests that further studies of the oral administration of amigen following gastro-duodenal hemorrhage are indicated and should be carried out. The Gastro-Intestinal Service in a large Army General Hospital does not have many cases of acute massive hemorrhage. They are usually seen in the station hospitals and have recovered from their hemorrhage by the time they reach the general hospitals. This study is reported, therefore, for the purpose of stimulating further investigation.

In summarizing these observations, it is apparent that the oral use of a mixture of amino acids in the treatment of peptic ulcer, especially in the presence of massive hemorrhage, has sound theoretical and experimental advantages; namely,

a. It acts as a buffer combining with acid, thus acting as an antacid.

b. It spares digestive activity on the part of the gastro-intestinal tract.

c. It is effective in treating the hypoproteinemia following massive hemorrhage. The daily administration of amino acids in amounts totalling 3.0 grams to 3.5 grams per kilo has proved more satisfactory, especially in the presence of a poor nutritional state; than the usual protein intake of 1.0 grams per kilo per day.

d. It contains all of the essential amino acids, is well tolerated by mouth, and is a source of adequate nitrogen for nutritional needs.

CONCLUSIONS

1. Eleven patients suffering a severe hemorrhage from peptic ulcer were treated with the usual Sippy diet to which was added a daily oral intake of from 100 to 200 gms. of a mixture of amino acids. The serum protein returned to normal, on the average, within 10.2 days. In a control group of six patients who were given the same Sippy diet but without the addition of the amino acids, the serum protein returned to normal, on an average, after nineteen days.

2. The treatment was well tolerated.

3. The importance of hypoproteinemia resulting from hemorrhage is discussed and emphasized.

The author wishes to express his thanks to Dr. Warren M. Cox, Mead-Johnson Co., Dr. Robert Elman, St. Louis, for their advice during this study and to Col. J. S. Sweeney, Chief of Medical Service, Bushnell General Hospital for his assistance in editing this paper.

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ACUTE PANCREATITIS

A Statistical Review of Recorded Experience

H. C. Robinson, M.D., and F. S. Alfenito, M.D.

From the Medical Department of Blodgett Memorial Hospital with the cooperation of Butterworth Hospital and St. Mary's Hospital, Grand Rapids, Michigan

INTRODUCTION

This survey of all records in the three Grand Rapids hospitals covers the nineteen year period from 1923 to 1942. There is no available documentation of cases of acute pancreatitis prior to 1923.

CLASSIFICATION

The analysis of these records seems to justify the separation of acute pancreatitis into acute hemorrhagic and acute non-hemorrhagic (interstitial or oedematous) pancreatitis. This is the classification used by Elman (1), although Abel (2) and others believe that acute oedematous pancreatitis is merely a step in the development of acute hemorrhagic pancreatitis. In this review we have arbitrarily classified the cases after a study of the records.

INCIDENCE

During this period of nineteen years 43 cases of acute pancreatitis were recorded. The incidence has increased in the last four years, 17 cases being seen in the first fifteen years. This seems to be only partly accounted for by increase in population. Since all but 5 cases either went to surgery or were autopsied it is not explained by improved diagnosis, unless surgeons previously neither recognized nor operated on these cases, which seems improbable.

There were 22 cases of hemorrhagic pancreatitis. Five were females and 17 were males. The age ranged from 31 to 73 years with an average age of 53 years. All had marital status except 1 single male whose age was 53 years.

There were 21 cases of non-hemorrhagic pancreatitis. Sixteen were females and 5 were males. The age ranged from 20 to 66 years with an average age of 45 years. All had marital status except 1 single female whose age was 29 years.

The incidence is relatively high in the fourth and fifth decades. Ten cases occurred between 20 and 40, twenty-four between 40 and 60, and nine between 60 and 80 years of age.

Hemorrhagic pancreatitis predominated in males and non-hemorrhagic pancreatitis predominated in females. Five females and 17 males had hemorrhagic whereas 16 females and 5 males had non-hemorrhagic pancreatitis, a marked sex reversal of incidence in the two groups.

ETIOLOGY

Of the 22 cases of hemorrhagic pancreatitis 16 came to surgery. Of these 10 had evidence of cholecystitis and 5 of the 10 had associated cholelithiasis. The six cases not subjected to surgery were autopsied and none showed evidence of biliary tract disease. Hence, 45 per cent of this series showed biliary tract disease. Six cases gave a previous history of cholecystitis and 1 had been subjected to a cholecystectomy.

Dragstedt (3) states that 60 per cent of his cases had associated bile tract disease. Abel (2) lists biliary tract infection as the most important contributing factor. He also mentions penetrating posterior duodenal ulcer. In 150 cases 18 per cent showed metaplasia of the pancreatic ductal epithelium.

Fifteen of the 21 cases of non-hemorrhagic pancreatitis went to surgery. Eleven of the 15 showed definite evidence of cholecystitis and 8 cases had associated cholelithiasis. One case was complicated by acute appendicitis and one unoperated case which came to autopsy had empyema of the gall bladder with cholelithiasis. Five of the 21 cases were assumed to be free from biliary tract disease on the basis of history.

In the records there was a past history of cholecystitis in 7 cases of the hemorrhagic and in 3 of the non-hemorrhagic group. It existed, however, in 50 per cent of the cases of the hemorrhagic group as against an incidence of at least 75 per cent in the non-hemorrhagic group.

Elman (1) found obstruction at the sphincter of Oddi universal in his operated cases of non-hemorrhagic pancreatitis. Westerman (4) lists obesity as an etiological factor in non-hemorrhagic pancreatitis.

PREVIOUS ATTACKS

Fifty per cent of the cases of hemorrhagic pancreatitis gave no history of previous similar attacks while the other 50 per cent gave a history of from one previous attack to repeated attacks over a period from 5 months to 12 years.

Six patients gave no history of duration of previous attacks and the remainder gave a history of attacks lasting from 1 to 13 days.

In the 21 cases of the non-hemorrhagic group, 12 gave no history of previous attacks and 9 gave a history of other attacks ranging over a period of from 1 to 17 years. One stated he had two previous attacks 14 and 17 years ago, respectively.

Ten cases gave no history of duration while in the remainder the time varied from "fleeting" to "a few hours."

Casberg (5) and Meyer May (6) both state that in hemorrhagic pancreatitis there is no history of previous attacks and in non-hemorrhagic pancreatitis there may be a history of previous attacks.

Our statistics on hemorrhagic pancreatitis are not in agreement with the statements of the afore-mentioned authors, as 50 per cent of the cases of hemorrhagic pancreatitis gave a history of repeated similar attacks over a period of from 5 months to 12 years.

PATHOLOGY

Of 14 autopsies in the hemorrhagic group, the pathological report showed 12 having hemorrhage into the pancreas. Fat necrosis was associated in 8 cases and in 2 cases necrosis was reported without gross evidence of hemorrhage. In 1 case necrosis was complete, the pancreas being "one necrotic mass."

Other findings appearing in the abdominal cavity at autopsy were peritonitis, interstitial hepatitis, biliary fistula, perforation of the stomach, duodenitis, and thrombosis of the pancreatic artery.

In the non-hemorrhagic group there was one autopsy which showed edema of the pancreas with some necrosis but the primary pathology was believed to be empyema of the gall bladder with lithiasis. This patient also had diabetes mellitus.

Nine cases had x-ray examinations in the hemorrhagic group. The studies carried out were either scout films, cholecystograms or gastro-intestinal series. In 1 case that had a gastro-intestinal study there was evidence of a "pressure defect in the 1st and 2nd portions of the duodenum, a narrowing of the distal 3rd of the duodenum and first 2 to 3 inches of the jejunum."

Frostberg (7) pointed out in 1938 that the head of the pancreas when enlarged produced an inverted 3 pattern along the second portion of the duodenum and had this been known it might have been helpful in this series.

In the non-hemorrhagic group 8 patients had x-rays during an attack and 3 had interval x-ray studies.

Two gastro-intestinal series taken during a severe attack showed enlargement of the duodenal curve in one and in the other a filling defect in the second portion of the duodenum. One study made during an interval showed what was believed to be an enlargement of the head of the pancreas.

One case or 8.5 per cent of those x-rayed in the hemorrhagic group showed some evidence of pancreatic involvement.

Twenty-five per cent of the non-hemorrhagic group which were x-rayed had evidence which might have been helpful in diagnosis.

In the hemorrhagic group the first white blood cell count taken ranged from 9,000 to 26,000 and the average, roughly, was 18,000.

In one case the white count on admission was 21,300. It fell two days later following surgery to 3,100 and again on the fifth post-operative day rose to 13,800. The initial differential count ranged from 76 per cent to 100 per cent polymorphonuclears with an average of 89 per cent. The red blood counts and the hemoglobin determinations were not significant.

In the non-hemorrhagic group the initial white blood cell count ranged from 6,400 to 36,500 with an average of 15,000. In 1 case the initial and highest white cell count was 6,400 with a differential count of 52 per cent polymorphonuclears. At one time the count dropped to 2,900. In this group the initial differential count ranged from 52 per cent to 96 per cent polymorphonuclears with an average of 78 per cent.

The findings in this series are in agreement with the findings of others; Gaither (8) states that the white count ranges from 15,000 to 25,000 cells and Casberg (5) states that the white cell count ranges from 15,000 to 20,000 on the second day of illness. In this survey we found a wider fluctuation of the white and polymorphonuclear cell count in the non-hemorrhagic group. The average count was somewhat higher in the hemorrhagic group.

Four fasting blood sugars were taken in the hemorrhagic group. The range was from 68 mgs. to 226 mgs. per 100 cc.

Six fasting blood sugars were taken in the non-hemorrhagic group. The range was 78 mgs. to 156 mgs. per 100 cc. The one exception was a diabetic who had a blood sugar of 444 mgs. per 100 cc.

Several authors have pointed out that the blood sugar level is often high in hemorrhagic pancreatitis and Friedenwald (9) and Roland (10) have found that the fasting blood sugar level is high in mild cases of non-hemorrhagic pancreatitis and apt to be low in the shock of the acute hemorrhagic type.

Blood amylase studies were not done on any of the hemorrhagic group.

In the non-hemorrhagic group the blood amylase level ranged from 330 to 3,982 units in 7 cases.

Somogyi (11) states that the normal serum amylase ranges from 70 to 150 units. Most authorities would agree that the serum amylase is elevated in both hemorrhagic and non-hemorrhagic pancreatitis but Elman, Arneson, and Graham (12) state that the serum amylase is low following gross pancreatic destruction.

There was nothing of significance in the urinary findings, except in 2 cases of each group bile was present in the urine.

SYMPTOMS AND SIGNS

While the onset was sudden with pain in by far the majority of cases, prior distresses were mentioned. These ranged from vague digestive disturbances to indefinite abdominal pains.

With the exception of 2 cases of hemorrhagic pancreatitis one of which had hematemesis and the other vomiting, all had sudden onset with pain.

In the series of non-hemorrhagic cases all had their onset with pain, except possibly 1 case which entered without a history in diabetic coma.

In all, except 4 cases of hemorrhagic and 2 cases of non-hemorrhagic

pancreatitis, the pain was described as severe. Other qualifying terms were sharp, dull, aching, steady, intermittent and cramp like.

Five cases had generalized abdominal pain, 3 had lower abdominal and 1 had low back pain in the hemorrhagic group. In all the others the pain was in the upper mid-abdomen and more often on the right than on the left.

In the non-hemorrhagic group there were a few cases with generalized abdominal pain and 1 with low back ache. The remainder had pain in the upper-mid-abdomen and again more often on the right than on the left.

Later the pain in both groups, while shifting perhaps, covered essentially the same areas but it was interesting to note that in 3 cases it moved to the symphysis pubis and in 1 case to the vagina.

There was radiation of pain in some cases. It was to the back and scapular region in a few cases. In one it was to the substernal and in another to the area of the left clavicle.

The next most common symptom was nausea which occurred in about one-third of the cases. Other symptoms were chills, heartburn, and polyuria.

Aside from abdominal pain the symptoms listed in the literature are various and inconstant and in this respect agree with those recorded in this series.

The area of maximum tenderness was in the mid-upper abdomen and more often toward the right than the left in both groups. One case only varied. In this instance the tenderness was around the umbilicus.

In the hemorrhagic group the tenderness was described as localized in 8 and generalized in 7 cases. One case had associated right costovertebral tenderness.

In the non-hemorrhagic group the tenderness was described as localized in 2 and generalized in 8 cases. Two cases had associated left costovertebral tenderness.

There were 4 hemorrhagic and 5 non-hemorrhagic cases with generalized abdominal spasm. In 2 non-hemorrhagic cases there was spasm localized to the right rectus muscle.

Five hemorrhagic and 5 non-hemorrhagic cases were reported to have generalized abdominal rigidity. Six hemorrhagic cases were described as having localized rigidity.

One hemorrhagic and 6 non-hemorrhagic cases had a palpable mid-epigastric mass.

Eighteen hemorrhagic and 12 non-hemorrhagic cases had abdominal distension of varying degree.

In this series the findings on examination of the abdomen are varied but mid-upper abdominal tenderness was most common.

Other signs noted were vomiting in over half the cases, constipation, diarrhoea and jaundice. In the hemorrhagic group there were 2 cases with cold perspiration and one with hematemesis recorded.

Where the bowel function was recorded early in the illness one of 15 cases was normal, all the others were constipated and 3 later developed diarrhoea.

In the hemorrhagic group the temperature range was from 97.2° to 102.4° with an average of 99.5°C.

In the non-hemorrhagic group the temperature range was from 98° to 104.4° with an average of 100.6°C.

Presumably, the lower average temperature in the hemorrhagic group can be accounted for because many of the patients were in varying degrees of shock. This is in essential agreement with the findings of men who have written on the subject.

The pulse in the hemorrhagic group ranged from 50 to 150 with an average rate of 109. The range was from 66 to 144 in the non-hemorrhagic group with an average rate of 107.

While the blood pressures were not all normal, there was nothing unusual or characteristic about the readings except in 3 cases where the pressure record was terminal and showed a very low pulse pressure.

TREATMENT

The treatment was supportive in all instances and in 16 of the 23 cases of the hemorrhagic group and 15 of the 21 cases of the non-hemorrhagic group which went to surgery, cholecystectomy or cholecystostomy was carried out.

PROGNOSIS

Twenty of the 23 cases in the hemorrhagic group died presumably of the disease.

In the non-hemorrhagic group, 4 of the 21 cases died. Of these, 1 was complicated by erysipelas, and 1 died of cancer of the urinary bladder with pancreatitis an incidental finding at autopsy. One died from peritonitis from a perforated stomach and another, expiring in diabetic coma, had empyema of the gall bladder and cholelithiasis co-existing revealed at autopsy.

SUMMARY

A survey of acute pancreatitis, covering the last 19 years and including all the cases on record in the three Grand Rapids hospitals has been made. They are arbitrarily classified as acute hemorrhagic and acute non-hemorrhagic pancreatitis on the basis of the recorded findings. There was a total of 43 cases. Twenty-two were hemorrhagic and 21 non-hemorrhagic. It occurred almost always in married people. In the hemorrhagic group about 75 per cent of the cases were males while in the non-hemorrhagic group about 75 per cent of the cases were females. The average age of attack in hemorrhagic pancreatitis was 53 and in non-hemorrhagic 45 years.

Fifty per cent of the hemorrhagic and 75 per cent of the non-hemorrhagic

series showed evidence of biliary tract disease. About 30 per cent in the hemorrhagic group and 14 per cent in the non-hemorrhagic group gave a history of previous attacks which, to the patient, seemed of a similar nature. The pathology found in the pancreas is implied in the classification. Eight per cent of those in the hemorrhagic and 25 per cent of those in the non-hemorrhagic group subjected to x-ray study gave diagnostic evidence had it been recognized.

The total white blood count averaged higher in the hemorrhagic group but in the non-hemorrhagic group it was subject to wide variations. There was a wide range, from low normal to high, in the fasting blood sugar level in both groups. The blood serum amylase level was elevated in the 7 cases of the non-hemorrhagic group on which it was done. The urine showed nothing of significance.

The onset of symptoms was almost always sudden. The first symptom was invariably severe abdominal pain usually in the upper right quadrant. There was invariably tenderness in the abdomen, usually in the upper right quadrant.

Approximately 70 per cent of each group had surgical intervention. The mortality rate was 87 per cent in the hemorrhagic and 19 per cent in the non-hemorrhagic series.

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THE PATHOGENESIS OF INTESTINAL POLYPS[1]

JOHN S. ATWATER, M.D.[2]
Fellow in Medicine, Mayo Foundation,
AND
J. ARNOLD BARGEN, M.D.
Division of Medicine, Mayo Clinic, Rochester, Minnesota

INTRODUCTION

The beginning of our present knowledge of polyps of the intestine came with the description by Menzel (14), in 1721, of a number of wartlike excrescences arising in a colonic mucous membrane which showed evidence of marked inflammation. His observations brought to light the problems inherent in polyposis which have been a source of concern to many observers since then; namely, the problem of carcinomatous change in the polyps, the problem of inflammation and the relation of one to the other.

The literature on this subject is too vast for review herein, nor is it essential to the study at hand, but since it forms rather an important background for this investigation, its high points are referred to in the bibliography which is appended (4, 9, 15, 19, 23).

A few of the early observers are worthy of special mention (10). Thus Wagner, Lebert (12), Luschka (13) and Virchow (20, 21) gave excellent descriptions of the gross and microscopic appearance of polyps. In 1881 Woodward (22) made clear that there were two kinds of polyps. Some he called true (primary) polyps while others he felt were secondary to chronic ulcerative colitis and these he named "pseudo-polyps." In the following year Cripps (5) described for the first time "multiple polyposis" of the colon associated with a hereditary factor. In cases of a brother and a sister, he reported the presence of many polyps, both sessile and pedunculated. He pointed out certain changes in the glandular characteristics which in the light of current knowledge suggest that he probably was observing the changes seen in adenocarcinomas of low grade.

Opinion concerning the pathogenesis of intestinal polyps has varied, and numerous hypotheses have had their day. Each one has had some support in scientific observation but each, in turn, has failed to meet all of the requirements to explain the formation and growth of polyps. To study the origin of polyps is, in essence, to study the formation of tumors itself. Ewing has summarized the histogenesis of carcinoma of the intestine and of ordinary

[1] Abstract of thesis submitted by Dr. Atwater to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements of M.S. in Medicine.
[2] Since this paper was written, Dr. Atwater has become Lieutenant (j.g.), M.C. V-(S) U.S.N.R.

benign intestinal polyps by stating that the transition in the early stages for one was essentially the same as that for the other.

The purpose of the study to be reported herein was to investigate the life of intestinal polyps from inception to full growth. An attempt has been made to demonstrate in progressive steps the changes which accompany this transition.

METHOD OF STUDY

The material studied was obtained at necropsy at the Mayo Clinic in the period between October, 1942 and February, 1943. Specimens were obtained from the colon in consecutive cases which came to necropsy during this period of time. The mucosa of the entire colon was examined with a hand lens within a few days after it had been placed in modified Kaiserling solution, number 1. Any region in which a change from the normal seemed present was cut and a specimen from it placed in formalin (10 per cent). In each case tissues were taken from the several portions of the colon as well as from any region which aroused suspicion. Serial sections were cut in several instances. In this manner, 1,046 sections were obtained from 241 colons. The van Gieson and Galantha mucin stains were used in many instances for more detailed examination.

The sections studied were divided into those used as controls and those displaying polyps. The former were of two types. (1) Specimens and sections obtained from colons in which no abnormality could be found either grossly or microscopically were designated as "pure" controls. (2) Some sections were obtained from colons in which polyps existed; the sections in this part of the control group were taken both adjacent to and distant from such polyps. Sections obtained from these colons were called "impure" controls.

The sections displaying polyps were divided into those showing benign polyps and those showing malignant polyps.

In this study, any structure protruding in abnormal fashion above the normal mucosa, sessile or pedunculated and having a glandular character was considered a polyp. Fibromas, myxomas, hemangiomas, lymphangiomas, lipomas or other benign tumors were not included.

INCIDENCE

Examples of reports of the incidence of colonic polyps are the following: Lawrence (11), in reviewing the records from about 7,000 necropsies stated the incidence to be 2.37 per cent in patients from thirty-two to fifty-six years of age. Susman (18) found 6 per cent to be the occurrence in his series of 1,100 necropsies. Stewart (17), in studying 1,815 cases in which necropsy was performed, gave the incidence at 4.19 per cent.

In the present series of 241 necropsies, 166 cases presented polyps. This is an incidence of 69 per cent. Evidently our use of a magnifying glass brought to light many tiny polyps which would be overlooked in the usual gross examination. Because of this the incidence is much higher than was expected or has been reported previously. In no instance was a mucosal projection considered a polyp unless there was adequate microscopic verification. Such protuberances were shown thus to be due to a change in the character of the epithelium and were not merely normal folds or mucosa thrown up by underlying lymph follicles.

CLASSIFICATION

The extent of the polypoid disease in each intestine was classified according to the method of one of us (J. A. B.) (1–3) as solitary polyp, multiple polyps, disseminated or diffuse varieties. Cases in which from two to six polyps were present in a single colon were included in the group called "multiple polyps." When more than six polyps were noted in a single colon, a disseminated variety of polypoid disease was considered present. In no instance of the disseminated type were the polyps limited to one anatomic segment of the large bowel. No cases of diffuse polyposis or congenital polyposis came under observation.

FACTORS OF AGE, SEX AND EXTENT OF POLYPOID DISEASE

Tissues from newly born infants to adults of ninety years of age were included in this study. No polyps were observed until the fourth decade of life, and the occurrence was greatest between the sixth and eighth decades. The mean age of the patients who did not harbor any polyps was fifty-one years, whereas the mean age of the patients harboring polyps was sixty-four years.

Saint (16) has stated that polyps occur in the ratio of 2.3 males to one female. Similarly, Lawrence (11) found the ratio to be 1.52:1.0. In our study, there were 3.18 males with polyps to each female but since the same proportion of males to females existed in the control group the difference in sex distribution seems to be of no significance.

Solitary growths occurred in 21 per cent of cases of malignant polyps; multiple polyps in 63 per cent and disseminated polyps in the remainder. In the cases exhibiting benign polyps, the incidence of solitary growths was greater and statistically was akin to that of multiple polyps; it was 46 and 48 per cent respectively. In the remaining cases of benign polyps disseminated polyposis was present.

In the group of malignant polyps, 85 per cent of the patients who had multiple polyps were males and the patients who had disseminated polyposis were divided equally between the sexes. Otherwise throughout the group, the sex distribution was similar to that of the controls.

In view of later findings, it is interesting to note that whereas the sessile form of polyp was seen in 57 per cent of the malignant group, it occurred in 91 per cent of the benign group.

ROLE OF LYMPHOID STRUCTURES

Examination of the literature for hypotheses concerning the pathogenesis of intestinal polyps revealed that changes in the primary epithelial structures and also in the subepithelial components had been suggested as responsible. Since investigators from time to time have indicated that lymphoid structures were involved, an evaluation of this factor was undertaken.

Since little direct evidence of change could be found in the diffuse lymphoid structure, examination of the discrete forms was undertaken. The lymph follicles were noted. Discrete or conglomerate follicles were found in 90 per cent of the sections obtained in cases labeled "pure controls," and in 70 per cent of the sections from benign polyps. Seventy-two per cent of the sections through sessile polyps and 82 per cent of those through pedunculated polyps also displayed similar follicles. The tendency was for the follicle to occupy portions of both mucosa and submucosa breaking through the muscularis mucosae. Individual follicles occurred separately above and below the muscularis as well. This was true in fully developed polyps and the adjacent microscopically normal mucosa also.

Secondary or so-called germinal centers and encapsulation of the follicles were found to occur equally in sections from controls and from the polyps. An increase in size or a change in the position of any follicle so that it extended upward through the mucosa to the lumen of the bowel was not remarkable in either control sections or polyps. It has been stated that such follicles rupture into the lumen of the intestine forming ulcers and that the adjacent epithelium prolapses into the spaces created. In the body's attempt to heal these breaks some glands are entrapped and polyps result. Ruptured follicles, resultant ulcerations (Schultze pattern), healed ulcers either with or without prolapsed epithelium and entrapped glands occurred with equal frequency in the sections from polyps and the sections used as controls. The hypothesis just mentioned concerning the role of the lymphoid structures in the pathogenesis of polyps, therefore, could not be substantiated by this study.

ROLE OF EPITHELIAL CHANGES

Other investigators have suggested that simple multiplication of the cellular epithelial components with resultant glandular hypertrophy was the earliest change in the development of polyps. Dukes (6, 7) has presented excellent schematic drawings to represent this concept. To evaluate such factors, all of the epithelial changes encountered were examined and tabulated.

It was found that in polyps there was thickening of the mucosa owing to elongation of the crypts of Lieberkühn. In 65 per cent of the malignant polyps these glands did not extend directly from the muscularis mucosae to the lumen of the intestine but were branched. The degree of ramification was related to the grade of malignancy. The higher the grade of malignancy, the greater the branching of the glands. Only an occasional section revealed such a change in the control series. A small number, 8.8 per cent, of the sections from benign polyps revealed branching, but all showed thickening of the mucosa with elongated glands.

In many instances the glands became enlarged with greatly widened alveolar lumina. Seventy-two per cent of the malignant polyps, 42 per cent of the benign polyps and only occasional examples in the control specimens presented this picture. In most of the malignant polyps the outlines of the glands displayed irregularity whereas such a change was present in only 38 per cent of the benign polyps.

Atypical epithelium, overlying a lymph follicle, occurred in from 13 to 17 per cent of all cases of polyps. Interestingly, it was noted three times more often in the polyps than in the controls.

With the hematoxylin-eosin stain, it was found that whereas almost all controls stained normally, there was variation in the staining of the polyps. Some polyps stained lighter and others heavier than normal. Ninety-one per cent of malignant polyps stained differently from normal; 82 per cent of these stained heavier than normal tissue. Two-thirds of the benign polyps stained like normal tissue and approximately a fourth stained more heavily than usual.

The cellular character changed progressively from that of the normal controls through that of the benign polyps to that of the malignant polyps. The cells became more irregular, decreased in height and gradually became cuboid. They gradually piled up in layers in a disorderly fashion. Mitotic figures were recognized far more frequently as the malignant change developed.

Normally the nucleus of each cell occupies a position in close approximation to the base of the cell. In the control specimens this was true. The nucleus was in normal position in only a third of the benign polyps and in a tenth of the sessile malignant polyps. In the pedunculated malignant polyps it was uncommon to find the nucleus in normal position and its size, shape and chromatin content had changed.

In from 50 to 63 per cent of all malignant polyps elevation of the nucleus was graded 1 on a grading basis of 1 to 4 in which 1 represents the least change and 4 the greatest. Whereas elevation of grade 2 did occur in 4 per cent of benign polyps, elevation of the nucleus of from grade 2 to 3 occurred in from a third to a half of the malignant polyps.

Production of mucus was decreased in three-quarters of the malignant polyps and in a third of the benign polyps. This observation was corroborated by the use of the Galantha mucin stain as well as by hematoxylin-eosin methods.

The greatest epithelial deviation toward carcinoma has been shown previously by Saint and others to occur more frequently in the peripheral portion of polyps away from the stem. This view was confirmed in the present study.

PATHOGENESIS

From this study it seems likely that the epithelium of the colon must pass through a chain of changes in the development of polyps. Figures 1, 2, 3 and 4 are presented in order to illustrate the changes from normalcy to malignancy. The primary change is epithelial (fig. 1). The reason why a localized patch of epithelium undergoes aberration from the normal is not evident. However, the existence of morphologic changes of varying degree is apparent.

The genesis is recognized earliest by more rapid proliferation of the epithelium at one site than in the neighboring epithelial elements. It is possible that this ability to proliferate is inherent in normal epithelium. If so, it would seem that some restraint or some inhibitory factor has been removed or attenuated and thereby an indefinite degree of overgrowth is made possible. At times such change proceeds to the point of pedunculation of the mucosa, possibly designed to afford a greater base and easier nutritional supply for the growing structure. When this occurs, a pedunculated so-called, benign polyp is formed.

The epithelium in the glands when the polyps first begin to develop exhibits primary hyperplasia (fig. 2). The cells retain their normal microscopic appearance and apparent physicochemical function such as production of mucus. The numerical increase results in an enlargement in the size of each crypt of Lieberkühn involved in the proliferative process. In order to accommodate for this increase the glandular structure itself must elongate. Limited by the muscularis mucosae and the subepithelial structures, this growth proceeds toward the lumen of the intestine. Such glandular hypertrophy becomes evident in a localized region in which the glands are taller and deeper than the neighboring normal structures. A tiny plaque or elevation is produced on the mucosal surface of the bowel.

From the observations of this study, other changes are seen to follow. In the process of accommodation to the overgrowth, the tubules often become branched. The cells multiply faster than a given segment of the structure can accommodate. The nuclei pile on each other (fig. 2*c*). They lose their normal position near the membrana propria and move outward toward the lumen of the tubule. An increasing proportion of cytoplasm appears between the nucleus and the base of each cell. The outline of the nuclei changes. Nuclei

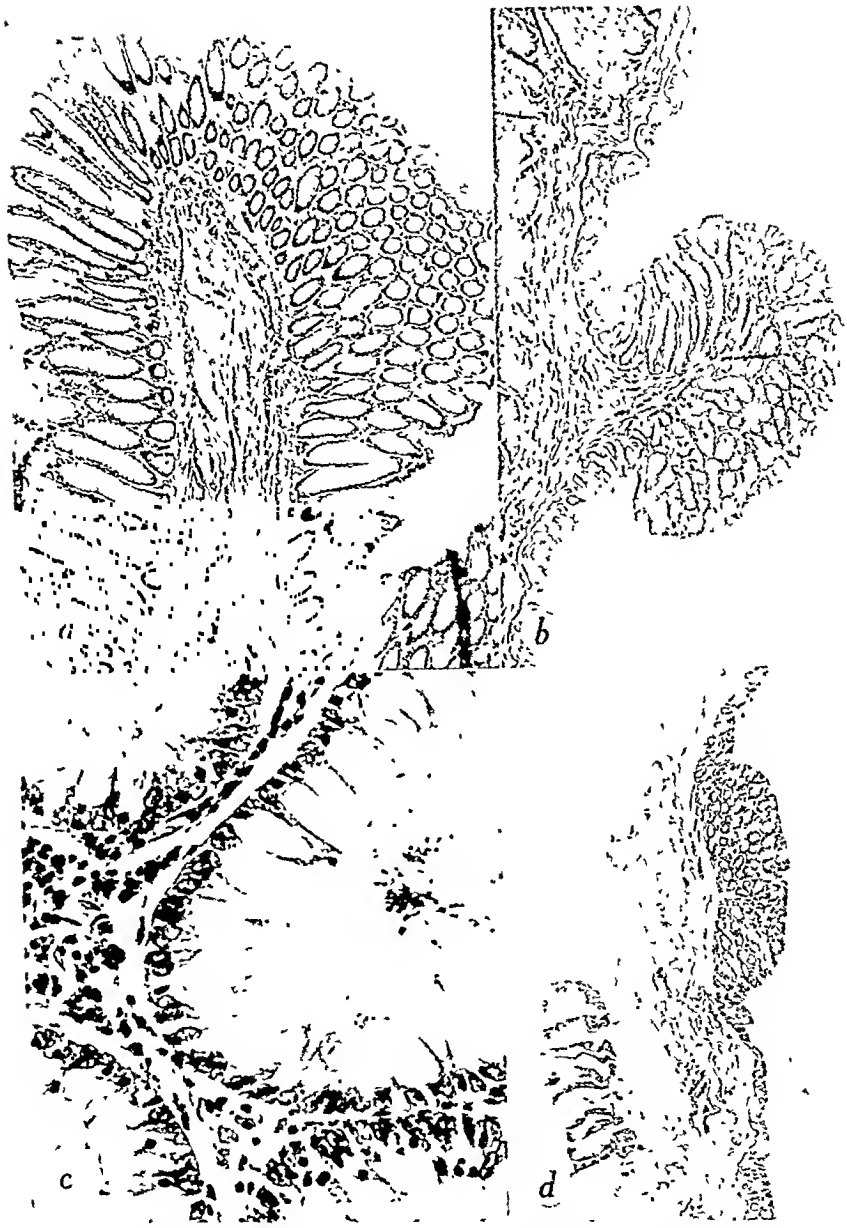

FIG 1 FIRST CHANGES IN THE DEVELOPMENT FROM NORMALCY TO MALIGNANCY

a Normal fold of rectosigmoidal tissue orderliness and uniformity of growth is evident (× 35).

b Benign polyp. The lengthened glands with deepened crypts, plentiful goblet cells, uniform staining and orderliness of arrangement may be noted (× 13)

c Higher magnification of an area shown in figure 1*b* Resemblance of glands and epithelium to normal may be noted Nuclei lie in close approximation to the basement membrane (× 340).

d Benign polyp Contrast hypertrophied lengthened glands comprising the mammillation with adjacent normal mucosa This represents one of the earliest changes seen (× 16)

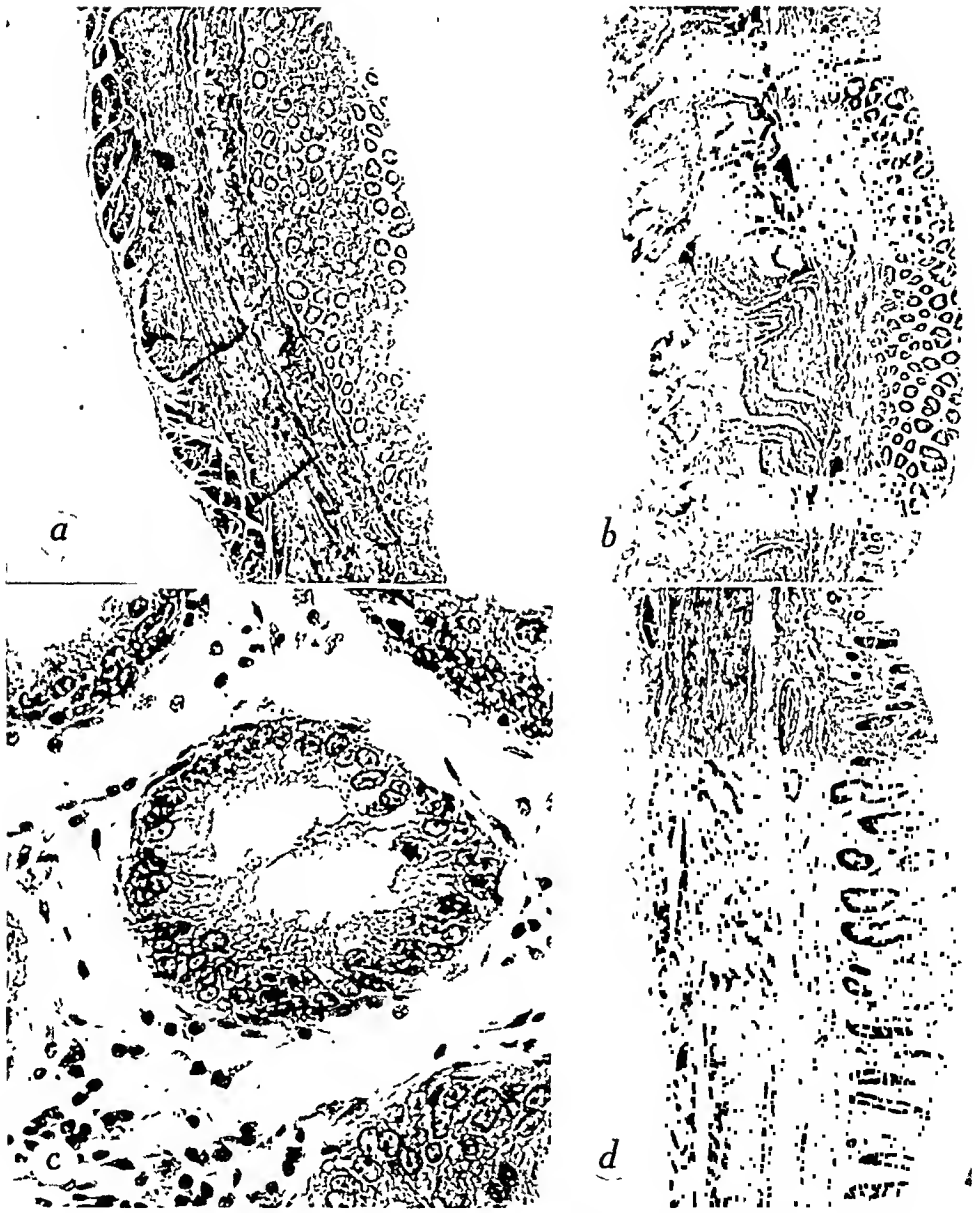

FIG. 2. LATER CHANGES THAN THOSE SHOWN IN FIGURE 1

a. Formation similar to that shown in figure 1*b*, except that along the surface of the intestine the epithelium has changed. It forms an "icing" of differently staining glands (× 18).

b. The "icing" has replaced the normal epithelium down to the muscularis mucosae. The cells stain more deeply. The glands are longer and tend to be irregular in outline. Production of mucus is not striking (× 13).

c. Higher magnification of an area shown in figure 2*b*. Changes should be contrasted with figure 1*a*. The cells are beginning to pile on each other. Many nuclei have moved away from the basement membrane and tend to be vesicular and irregularly shaped. The boundaries between the individual cells are indistinct. Production of mucus is meager. Mitotic figures are more evident (× 340).

d. The lengthening of the individual glands is displayed together with the changes noted in figure 2*b* (× 21).

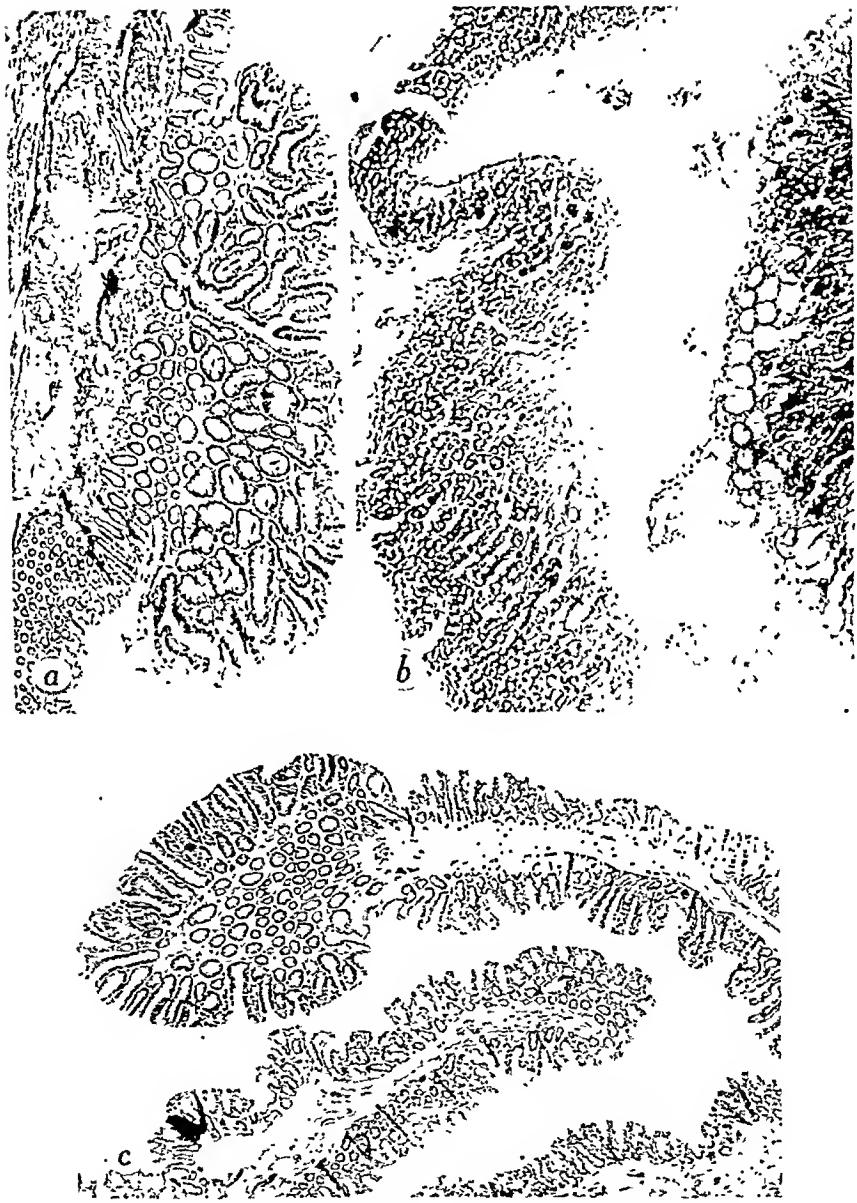

FIG. 3 LATER DEVELOPMENT THAN THAT SHOWN IN FIGURE 2

a. Deeper staining of polyp as contrasted with neighboring normal epithelium, branching of glands and enlarged irregular alveoli (× 15).

b. Higher magnification of an area shown in figure 3*a* Cells have lost their individuality, nuclei are heaped on each other and are irregular in shape. Irregularity of chromatin is present, some nuclei are vesicular while others stain black. Nuclei have moved further away from the basement membrane than in figure 2*c*. Production of mucus is minimal (× 220).

c. The epithelial change at the tip of a long fold Nearby is a fold without the epithelial change. Attention is called to the blacker staining of the area of change and the decrease in number of goblet cells in that area (× 17).

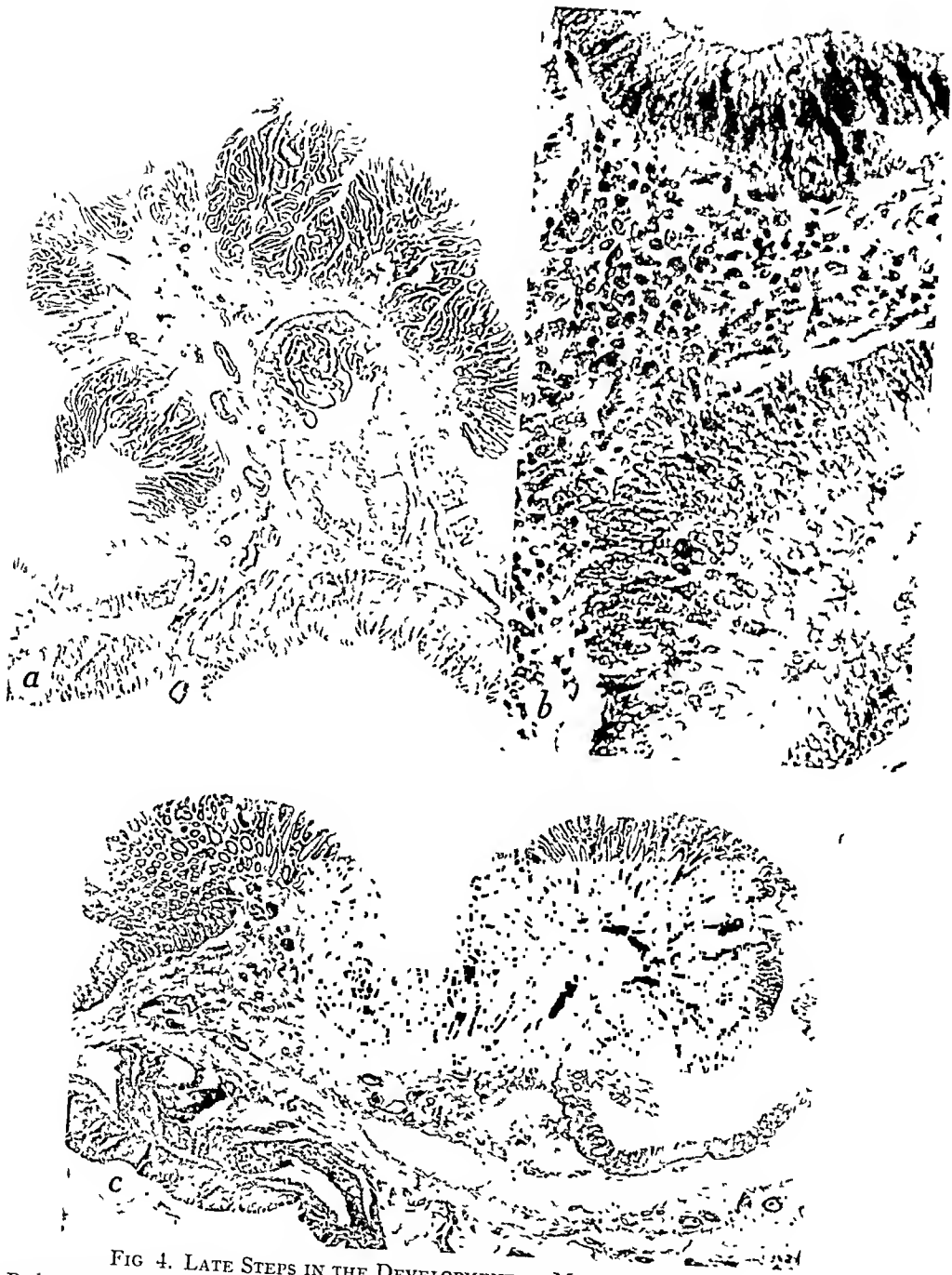

FIG 4. LATE STEPS IN THE DEVELOPMENT OF MALIGNANT POLYPS

a. Pedunculated polyp mucosa is normal along the base and area adjacent to polyp. The height, regularity, staining characteristics and mucus production of the normal mucosa should be contrasted with that of polyp Changes illustrated in figures 1, 2 and 3 exist here in exaggerated form.

b. Higher magnification of an area in figure 4*a* Normal appearing mucosa is absent. The nuclei form a heterologous mass They have disregarded the normal basement membrane and are seen streaming into the glandular interstices (× 220)

c. More extensive change may be noted in this polyp with two polypoid divisions (× 11).

frequently lose their fusiform shape and become spherical. Polyhedral irregular nuclei are prominent.

The chromatin content of the nuclei increases (fig. 3) in many cells. In others a vesicular character becomes evident. Mitotic figures are found more frequently. The columnar shape of the individual cell gradually is lost and a more cuboid form is assumed. Cells lose their normal alinement and eventually present as a heterologous group with no regularity of position. The outlines of the glands become irregular.

The ability of the cells to produce mucus is lessened gradually. Some glands are devoid of mucus as visualized by mucin staining technic; others show goblet cells to be present but in progressively decreasing numbers.

The cells stain differently from normal cells and the degree of change from the normal is in direct proportion to the amount of cellular aberration. If simple hyperplasia only is present, staining usually is like that of normal cells. A small percentage of benign polyps display variation in their ability to stain with hematoxylin-eosin stain. As the cellular and nuclear changes increase, the divergence from the staining characteristics of normal tissue is greater. In the majority of instances the cells stain more deeply, although a few are lighter than normal.

At the site of primary hyperplasia and in the benign polyps the basement membrane is intact. However, as the series of epithelial changes progress there is a disrespect for the basement membrane and the cells burst through it and seemingly flow into the glandular interstices (fig. 4).

When these changes are well established, not only has lack of respect for the basement membrane occurred, but also the muscularis mucosae no longer serves as a barrier. The cells spread freely and in an uninhibited fashion into the subepithelial tissues. Glandular structures may, or may not, be retained when this occurs.

Minimal change is noted in the mucosal stroma until the larger polyps have been formed. At that time the polyps are frequently the seat of inflammatory changes and small hemorrhages. Necrosis within the polyp may be present.

The presence, or absence, of these changes forms a pattern. This pattern depicts an epithelial transition progressive from the normal, through the so-called benign polyps, to the various degrees of cellular dedifferentiation as present in frank malignancy.

COMMENT

From our study the following points seem significant:

1. It was possible to trace the pathogenesis of intestinal polyps from the earliest epithelial change to frank carcinoma. One way in which polyps are formed is through epithelial change.

2. The incidence of colonic polyps including tiny sessile lesions was 69 per cent in the 241 cases studied.

3. No difference was found in the occurrence of polyps in the two sexes.

4. The mean average age of patients harboring polyps in our series was sixty-four years.

5. Lymphoid structures at most seem to play only a casual role in the pathogenesis of intestinal polyps.

In view of our evidence and its abundant verification in clinical experience, it would seem that the term "benign polyp" should not give the idea of an innocent tumor but rather of one stage in the pathogenesis of a carcinoma about which eventually there will be no question.

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BICARBONATE AND CHLORIDE OF PANCREATIC JUICE SECRETED IN RESPONSE TO VARIOUS STIMULI

WM. M. HART, PH.D.[1] AND J. E. THOMAS, M.D.

From the Dept. of Physiology of the Jefferson Medical College of Philadelphia

INTRODUCTION

It is well known that the concentration of enzymes in pancreatic juice varies over a wide range depending on the stimulus used to provoke secretion (18, 16, 7). On the other hand we know little or nothing about the possible variations in bicarbonate and chloride content of pancreatic juice that may result from the use of different stimuli.

Walther (18) and Babkin and Savich (2) have reported slight differences in the total inorganic matter (ash) of pancreatic juice associated with differences in enzyme content brought about by the use of different secretory stimuli. Additional data, less closely related to the problem under discussion, are available from the studies of Gamble and McIver (5), Ball (3), Lim, Ling, Liu and Yuan (10), and Komarov, Langstroth and McRae (9). It appears from these studies that the bicarbonate concentration of pancreatic juice tends to increase with increasing rate of secretion whereas the chloride concentration varies in the opposite sense, the sum of the two being approximately constant.

All of the studies referred to have been made on either anesthetized animals or animals with permanent pancreatic fistulas. Neither is entirely suitable for the purpose in as much as the inorganic constituents of the secretion may be modified by the changes in permeability of cellular membranes and in acid-base balance that probably occur under these artificial conditions. The development of a new method, to be described presently, which is free from these objections has made possible a more satisfactory approach to the problem. We have, therefore, considered it worth while to repeat some of the older work while investigating some of the hitherto neglected aspects of the subject.

METHODS

The pancreatic juice was collected from unanesthetized dogs, which had permanent gastric and duodenal fistulas fitted with tubes made of metal and hard rubber (15). The duodenal fistula was placed opposite the main pancreatic duct. To collect pancreatic juice, a temporary cannula was inserted into the duct by way of the fistula tube as suggested by Scott and his coworkers (14).[2] By this method pure pancreatic juice was obtained from ani-

[1] Present address, Temple University, Philadelphia.

[2] Tuckerman (17) cannulated the pancreatic duct through a tubulated fistula of the duodenum but the fistula tube and cannula which he used were awkward in shape and unsuited to the purpose. Consequently, the method was regarded as impractical until Scott, using a fistula tube of the type used in this study and an olive-tipped metal cannula of his own design, proved that the duct could be cannulated without difficulty and the cannula kept in place for as long as might be necessary. We are indebted to Dr. Scott for instruction in the use of his method and a gift of one of his cannulas. More recently we have preferred to use glass cannulas of the type illustrated in figure 1. They are essentially similar in design to Scott's metal cannula.

mals which retained all their digestive secretions except for the occasional 5 to 20 cc. sample taken for study, and in which the normal anatomical relations of the pancreas, including its complete nerve supply, were preserved.

The individual samples were collected without contact with air into a glass syringe connected with the cannula through a narrow rubber tube. The syringe was supported in a vertical position, plunger down, so that when the tip of the syringe was open the plunger would fall out of its own weight. The plunger was lubricated with distilled water. When the syringe was connected with the cannula the plunger was displaced by the secreted juice aided by gravity. To avoid undue contamination of the sample with water used to lubricate the syringe the first two to five cc. collected were always expelled from the syringe, along with any air that might be present, and discarded.

Analysis of the samples was begun as soon as possible after collection, usually within the first half hour. Transfer to the measuring pipette was made directly from the syringe through a short rubber connection after discarding the contents of the connecting tube. At no time was any part of the pancreatic juice used for analysis exposed to even minimal quantities of air.

Various substances were used to elicit a flow of pancreatic juice, including HCl, glutamic acid, peptone solutions, and solutions of soap.[3] These were either injected into the upper intestine intermittently in measured amounts or allowed to flow in from a Mariotte's bottle or from a motor drive injection pump. In a few experiments secretin was given intravenously. In some instances peptone was added to the soap or HCl used as stimulus in an effort to increase the nitrogen content of the secretion. Acid was also occasionally added to peptone to increase the rate of secretion. All such instances are indicated by appropriate notations in the tables.

Some of the animals used had been subjected to other experimental procedures which must be mentioned although they did not appear to influence the results. In dog 2-40 the common bile duct was transplanted into the stomach four years previous to this study. In dog 7-43 the splanchnic nerves had been severed two years previously. They had doubtless regenerated. Dog 9-43 had a Thiry-Vella loop of the jejunum. Some of the samples were collected after administering atropine or hyoscyamine. These drugs had no effect on the bicarbonate concentration of the pancreatic juice except indirectly through changes in rate of secretion.

Total carbon dioxid was determined by the manometric method of Van Slyke and Neill. The Guest precision pipette was used to deliver 0.2 ml. of pancreatic juice into the chamber (12). Gas volumes were reduced to 2 ml.

[3] HCl solutions ranged from N/10 to N/40; glutamic acid solutions were saturated at room temperature, approximately 2 per cent; peptone solutions were generally 5 per cent "Bacto Protone" in 0.6 per cent NaCl; soap solutions were 2 per cent "Ivory Snow" in N/100 HCl (pH 9.5).

Duplicate determinations agreed within 0.3 millimoles. Bicarbonate values were calculated by means of the Henderson-Hasselbach equation, taking pK′ as 6.1. This figure for pK′ was used following the assumption of Ball that the ionic activity of pancreatic juice is probably similar to serum. A Leeds and Northrup "pH indicator" was used for pH determinations. The glass electrode was placed in a closed cell of 4 ml. capacity. No effort was made toward exact control of temperature but all determinations were made at approximately 25°. Half the chloride determinations were made by the diffusion method of Conway (4). This method was then abandoned for the more rapid adsorption indicator technic of Saifer and Hughes (13). The micro-Kjeldahl procedure was used for nitrogen estimations.

RESULTS

Explanation of tables: The analytical data and the results of calculations based on them are presented in the tables (1–7). Table 1 deals with special experiments which will be described in the subsequent text. The data are divided among the remaining tables according to the method or stimulus used to elicit pancreatic secretion. The rate of secretion is given in cc. of pancreatic juice secreted per minute per kilogram weight of dog (cc./m./k.). This value was found to give better agreement among the several animals than the simpler "cc. per minute" commonly used. To save space the year has been omitted from the "date" column. The work was done in late 1943 and early 1944. The other notations follow the usual conventions.

Relation of chloride and bicarbonate.[4] Previous observations to the effect that the concentrations of chloride and bicarbonate in pancreatic juice bear a reciprocal relationship to each other were confirmed. The sum of their concentrations (in milliequivalents per liter) is approximately constant and isoosmotic with the blood (165 milliequivalents for the dog). In one experiment the bicarbonate concentration of the juice was 152.4 m.M./L., while the concentration of chloride was 11.2 m.M./L. (sum 163.6). In another experiment, the bicarbonate concentration was 74.5 m.M./L., while the chloride concen-

[4] The values for "bicarbonate" given in the tables include carbonate. The amount of bound carbon dioxid present as carbonate in pancreatic juice is small. This may be determined from the equation

$$\frac{[B_2CO_3]}{[CO_2]} = \frac{1}{1 + \frac{[H^+]}{K'}}$$

where K'_2, the apparent second dissociation constant of carbonic acid, is 1.6×10^{-10} at 38°. At the highest value for pH in our data (8.3) 3 per cent of the bound carbon dioxid is present as carbonate. Ball calculated that at pH 8.24, 1 per cent of the bound carbon dioxid was carbonate. However, the value 10.22 (0.6×10^{-10}) was used for pK'_2. This value actually represents pK_2 or the thermodynamic value with zero electrolyte. The apparent second dissociation constant is related to the ionic strength of the solution as $pK'_2 = 10.22 - 1.1\sqrt{\mu}$ where μ is the ionic strength (8).

tration was 90 m.M./L. (sum 164.5). The sum of bicarbonate and chloride values in the various tables ranges from 154 to 175. It will be noted, however, that only three are above 170 and six are below 160. Twenty-one fall between 160 and 170 with the median at 164.

Failure of the stimulus to influence chloride and bicarbonate: Since the concentrations of chloride and bicarbonate in pancreatic juice summate to give a nearly constant value, we may select one for attention and regard the other as the dependent variable. Choosing the bicarbonate it can be shown from the data that its concentration remained independent of the stimulus used to promote secretion.

This fact may not be immediately apparent because the bicarbonate concentration of pancreatic juice varies with the rate of secretion and each stimulus

TABLE 1

The results of special experiments showing lack of correlation between total CO_2 in pancreatic juice and the stimulus used to provoke secretion when the rate of secretion is constant

DATE	DOG NO.	STIMULUS	N	COLLECTION TIME	VOLUME	RATE OF SECRETION	CO_2
			mg./cc.	*min.*	*cc.*	*cc./m./k.*	*mM/L.*
12/24/43	7-43	Acid Peptone	1.12	16	15	0.059	146.25
12/24/43	7-43	HCl	0.45	16	16	0.062	143.44
12/27/43	2-40	Peptone	7.42	30½	10	0.016	69.36
12/27/43	2-40	HCl	1.22	32½	10	0.015	81.91
1/ 4/44	2-40	Soap + Peptone	2.20	9	10	0.055	136.38
1/ 4/44	2-40	HCl	0.66	9½	10	0.052	142.67
1/ 8/44	7-43	Peptone	5.70	47	9	0.0119	88.06
1/ 8/44	7-43	HCl	0.59	30	6	0.0125	110.35
1/10/44	2-40	Peptone (Witte's)	2.80	7	10	0.071	131.79
1/10/44	2-40	HCl	0.59	12	9	0.037	128.53
1/10/44	2-40	Peptone (Witte's)	3.78	12	9	0.037	123.42
1/15/44	7-43	HCl	1.26	41½	10	0.015	105.78
1/15/44	7-43	Soap	2.48	45	10	0.014	121.32

tends to cause secretion at a characteristic rate, different from that of the others; for example, peptone tends to induce a slow rate of secretion, acid a high rate. Naturally a majority of the peptone samples will have a bicarbonate content characteristic of a low rate of secretion and the acid samples will reflect the influence of the more rapid secretion typical of the response to acid. So far as the data as a whole are concerned the situation is further complicated by differences in animals and possible variations in one animal from day to day. Nevertheless it is evident from figure 2 that all the data from one animal tend to approximate the same curve regardless of the stimulus.

In the hope of eliminating some of the extraneous variables, experiments were performed in which an attempt was made to obtain successive samples from the same animal with different stimuli at the same rate of secretion. When we were successful in this, the bicarbonate content of the successive

samples was strikingly similar. Illustrative experiments of this type are recorded in table 1.

TABLE 2

Results of analysis of pancreatic juice collected with HCl as the stimulus

DATE	DOG NO.	RATE OF SECRETION	CO_2	HCO_3	Cl	$HCO_3 + Cl$	pH	N	COLLECTION TIME	VOL.	$\frac{HCO_3}{Cl}$
		cc./m./k.	*millimoles per liter*					*mg./cc.*	*min.*	*cc.*	
10/26	2-40		133.3	132.0	29.7	161.7	8.12	1.19	10	(?)	4.5
10/26	2-40		128.6	127.3	34.0	161.3	8.20		10	(?)	3.7
12/17	2-40	0.0741	138.9	137.5	26.9	164.4	8.29	0.35	8	15	5.1
12/17	2-40	0.0189	116.1	115.0	45.4	160.4	8.15	0.57	25	12.75	2.5
*12/20	2-40	0.0593	128.1	126.8	36.4	163.2	8.30	0.70	10	16	3.5
12/20	2-40	0.0667	129.2	127.9	36.8	164.7	8.31	0.28	10	18	3.4
12/23	2-40	0.0448	133.2	131.9			8.25	0.42	15	19	—
*12/23	2-40	0.0370	121.8	120.5			8.22	1.82	15	15	—
12/29	2-40	0.0741	139.3	138.0			8.28	0.45	5½	10	—
12/29	2-40	0.0530	138.5	137.0			8.28	0.75	6¾	10	—
10/22	7-43	0.0206	140.6	139.5	26.0	165.5	7.92		45	15±	5.3
11/2	7-43	0.0412	137.2	135.8			8.25	0.95	30	20	—
11/26	7-43	0.0169	125.3	124.0	44.0	168.0	8.20		55	15	2.8
12/16	7-43	0.0250	125.3	124.0	30.5	154.4	8.16	0.98	30	12	4.1
12/16	7-43	0.0494	140.7	139.3	22.0	161.3	8.23	1.40	15	11.9	6.1
12/18	7-43	0.0362	146.3	144.8	21.6	166.4	8.25	0.56	15	13	6.8
†12/18	7-43	0.0338	139.2	137.8	29.6	167.4	8.19	1.01	18½	10	4.7
12/22	7-43	0.1038	158.6	157.0	17.9	174.9	8.20	0.84	6	10	8.7
12/22	7-43	0.0694	154.0	152.4	11.2	163.6	8.18	0.70	9	10	13.6
*12/22	7-43	0.0412	152.0	150.5	21.5	172.0	8.18	0.98	15	10	7.1
*12/24	7-43	0.0625	146.2	144.8	21.5	166.3	8.19	1.12	16	15	6.9
12/24	7-43	0.0625	143.4	142.0	17.6	159.6	8.21	0.45	16	16	8.3
12/28	7-43	0.0150	105.8	104.7			8.03	1.26	41½	10	—
‡12/28	7-43	0.0137	121.3	120.1			8.10	2.48	45	10	—
1/ 7	7-43	0.0137	115.2	114.0			8.06	1.26	46	10	—
1/ 7	7-43	0.0150	119.0	117.8			8.10	1.22	41	10	—
5/17	7-43	0.0312	144.9						10	5	—
5/12	1-44	0.0625	150.8						8	10	—
§5/13	1-44	0.0555	140.9						9	10	—
11/30	9-43		139.6	138.2			8.13	0.56	21	18	—
12/14	9-43		139.9	138.5	21.8	160.3	8.19	1.29	18	15	6.2
12/15	2-40	0.0705	142.0	140.6	23.0	163.6	8.28	0.28	9	17	6.0
12/30	9-43		139.7	138.3			8.24		11¼	10.1	

* With Peptone.

† Dog vomited during collection; blood CO_2 = 24 mM./L. (53 vol. %).

‡ With Soap.

§ After Atropine.

Relation of bicarbonate to total nitrogen: The values for total nitrogen were found to be unrelated to the rate of secretion or the concentration of bicarbonate in the juice. When plotted against either of the latter variables the values for total nitrogen are widely scattered.

Relation of bicarbonate to rate of secretion: At rates of secretion below 0.05 ml. per minute per kilo., the concentration of bicarbonate in the pancreatic juice was found to vary directly with the rate of secretion. The values found at the lower rates of secretion suggest an approach to the blood level for bicarbonate at zero rate. In one experiment (dog 2-40), by slow infusion of glutamic acid, a rate of 0.059 ml. per minute (0.0029 ml./m/k.) was obtained. The concentration of total carbon dioxid in this specimen was 35 m.M./L. At a rate of about 0.05 ml./m/k. the bicarbonate concentration reached a maximum and

TABLE 3

Stimulus, glutamic acid

DATE	DOG NO.	RATE OF SECRETION	CO_2	COLLECTION TIME	VOLUME
		cc./m./k.	*mM./L.*	*min.*	*cc.*
5/22	2-40	0.0022	35.0	67	4
5/22	2-40	0.0464	135.5	4	5
5/22	2-40	0.0318	115.0	7	6
5/23	7-43	0.0125	100.0	24	5
5/23	7-43	0.0562	148.1	11	10
5/25	1-44	0.0414	125.2	12	10
5/25	1-44	0.0185	103.8	13½	5
5/25	1-44	0.0110	72.4	23	5
5/26	1-44	0.0055	65.7	30	3.4
5/26	1-44	0.1000	146.3	2½	5
5/26	1-44	0.0830	142.3	3	5
5/26	1-44	0.0235	122.9	10½	5
5/27	1-44	0.0205	98.9	12	5
5/27	1-44	0.0055	90.9	25	2.8
5/27	1-44	0.0225	107.5	11	5
5/31	1-44	0.0160	105.7	15½	5
6/3	1-44	0.0710	151.0	3½	5
6/3	1-44	0.0255	107.0	9¾	5
6/3	1-44	0.0344	145.0	7¼	5
6/3	1-44	0.0330	123.0	7⅓	5
6/3	1-44	0.0450	141.4	5½	5
6/3	1-44	0.0330	135.0	7½	5
6/3	1-44	0.0355	138.5	7	5

further increase in the rate did not alter the concentration. The maximum bicarbonate concentration tended to be the same in any one animal from day to day but differed in the different animals, ranging from 135 to 148 m.M./L. These facts are illustrated in figure 2.

pH of pancreatic juice: The pH of the pancreatic juice in our series ranged from 8.00 to 8.30. Juices of low bicarbonate content, in general had a pH close to 8.00 while those of high bicarbonate content approached 8.30. When pH is plotted against bicarbonate a moderate scatter of points is noted in the

data as a whole but those from a particular animal fall into a more distinct line. Besides difference in animals, variations in protein content, unrelated to the bicarbonate content, doubtless influence the pH.

TABLE 4

Stimulus, peptone

DATE	DOG NO.	RATE OF SECRETION	CO_2	HCO_3	Cl	HCO_3 + Cl	pH	N	COLLECTION TIME	VOL.	$\frac{HCO_3}{Cl}$
		cc./m./k.	*millimoles per liter*					*mg./cc.*	*min.*	*cc.*	
10/28	2-40	0.00853	73.6	72.8	81.3	154.1	8.00	5.67	65	15±	0.9
10/23	2-40	0.0129	62.0	61.0			8.06	8.12	42+	15±	
11/1	2-40	0.0148	75.3	74.5	90.0	164.5	7.88	7.00	37	15	0.8
11/22	2-40	0.00853	72.8	72.1	89.1	161.2	8.05	7.14	65	15	0.8
12/27	2-40	0.0122	69.4	68.6			8.00	7.42	30½	10	—
*12/27	2-40	0.0111	81.9	81.0			8.02	1.22	32¾	10.1	—
1/10	2-40	0.0259	131.8	130.5			8.20	2.80	10	7	—
*1/10	2-40	0.0278	128.5	127.2			8.20	0.59	12	9	—
1/10	2-40	0.0278	123.4	122.2			8.25	3.78	12	9	—
†5/19	2-40	0.00853	98.3						15	3.5	—
†5/26	2-40	0.0185	97.4						10	5	—
5/30	2-40	0.0141	87.1						13	5	—
10/25	7-43	0.0125	83.6				8.10	8.55	77+	15±	—
11/23	7-43	0.0131	90.3	89.4	74.7	164.1	8.08	6.30	70	15	1.2
1/8	7-43	0.0106	88.0	87.2			8.00	5.70	47	9	—
*1/8	7-43	0.0125	110.3	109.2			8.06	0.59	30	6	—
†5/11	7-43	0.0625	149.0						10½	10	—
5/17	7-43	0.0218	126.6						14	5	—
*5/30	7-43	0.0518	135.9						6	5	—
*5/30	7-43	0.0238	104.5						13	5	—
‡6/2	7-43	0.0832	148.6						7½	10	—
‡6/2	7-43	0.0732	148.0						8½	10	—
6/2	7-43	0.0106	86.2						29	5	—
5/10	1-44	0.0135	113.6						18	5	—
5/12	1-44	0.0115	119.3						21½	5	—
5/12	1-44	0.0125	121.2						20	5	—
5/16	1-44	0.0140	60.1						18	5	—
†5/27	1-44	0.0275	124.3						9	5	—
5/29	1-44	0.0115	69.0						22	5	—
5/29	1-44	0.0155	108.2						16	5	—
*5/29	1-44	0.0145	114.0						17	5	—
*‡5/31	1-44	0.0115	84.1						22	5	—
*‡5/31	1-44	0.0115	80.0						22	5	—

* With HCl.

† After atropine.

‡ After hyoscyamine.

The range of pH values in our data is much narrower than some previously reported. Our experimental conditions were probably sufficiently varied to cover the entire normal range. In view of the low CO_2 tension of pancreatic

TABLE 5

Stimulus, soap

DATE	DOG NO.	RATE OF SECRETION	CO_2	HCO_3	Cl	HCO_3 + Cl	pH	N	COLLECTION TIME	VOL.	$\frac{HCO_3}{Cl}$
		cc./m./k.	*millimoles per liter*					*mg./cc.*	*min.*	*cc.*	
11/24	2-40	0.0329	123.0	121.7	49.9	171.7	8.23	2.48	19	16.5	2.4
11/29	2-40	0.0370	120.6	119.4	44.5	163.9	8.22	1.54	16	16	2.7
12/2	2-40	0.0189	125.1	123.9			8.23	1.40	31	16	—
12/29	2-40	0.0615	135.9	134.5			8.24	0.59	6	10	—
12/29	2-40	0.0615	140.1	138.7			8.28	0.52	6	10	—
* 1/4	2-40	0.0411	136.4	135.0			8.29	2.20	9	10	—
† 1/4	2-40	0.0411	142.7	141.2			8.32	0.66	9½	10	—
† 1/4	2-40	0.0152	96.8	95.9			8.13	1.36	24	10	—
* 1/5	7-43	0.00593(?)	83.8	82.9			7.97	8.57	63	10	—
1/18	2-40	0.00926	64.2	62.9			7.86		39	10	—
1/18	2-40	0.0285	113.9	112.8			8.10		12½	10	—
10/29	7-43	0.0187	114.3	113.1	45.2	158.3	8.12	3.92	50	15±	2.5
12/1	7-43	0.0206	128.2	127.0			8.18	2.90	45	14.5	—
5/17	7-43	0.0238	122.8						13	5	—
1/14	9-43		140.2				7.64(?)	1.85	16	10.1	—
1/17	9-43		110.5	109.5			8.10		32	10	—
1/17	9-43		132.3	131.0			8.19		11½	10	—
1/17	9-43		133.5	132.1			8.19		10½	10	—

* With peptone.
† With HCl.

TABLE 6

Stimulus, secretin

DATE	DOG NO.	RATE OF SECRETION	CO_2	HCO_3	Cl	HCO_3 + Cl	pH	N	COLLECTION TIME	VOL.	$\frac{HCO_3}{Cl}$
		cc./m./k.	*millimoles per liter*					*mg./cc.*	*min.*	*cc.*	
12/4	2-40	0.0325	123.7	122.5	39.8	162.3	8.19	0.56	16½	15	3.0
12/4	2-40	0.0442	126.8	125.5	37.6	163.1	8.19	0.31	14½	16	3.3
12/15	2-40	0.0259	135.2	133.8	25.2	159.0	8.26	0.56	24	16.5	5.3
5/16	2-40	0.0204	116.5						9	5	—
12/3	7-43	0.0436	142.7	141.2	25.7	166.9	8.25	0.80	28	19.5	5.4
5/13	7-43	0.125	148.4						2½	5	—
12/14	9-43		134.5	133.2	23.4	156.6	8.19	0.98			5.7

TABLE 7

"Spontaneous" secretion

DATE	DOG NO	RATE OF SECRETION	CO_2	COLLECTION TIME	VOLUME
		cc./m./k.	*mM/L.*	*min.*	*cc.*
6/1	1-44	0.0075	53.2	34	5
6/1	1-44	0.0035	44.8	70	5

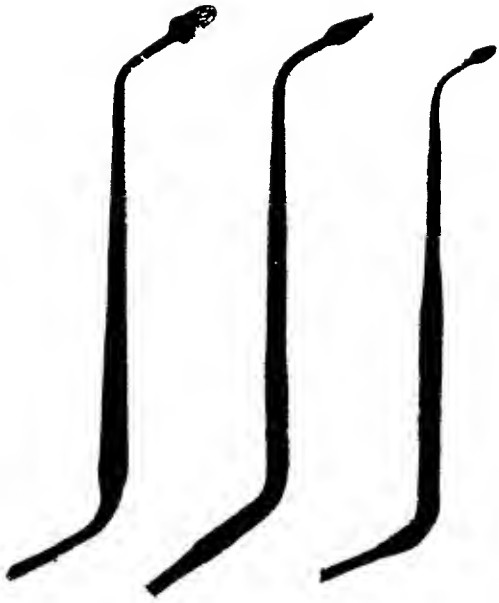

FIG. 1. GLASS CANNULAS USED TO CANNULATE THE PANCREATIC DUCT THROUGH A DUODENAL FISTULA

The cannulas were filled with a white paste before being photographed. The bend at the outer (lower) end facilitates handling and prevents kinking of the rubber collecting tube. This tube does not hang free but is pinned up in the middle to some part of the harness supporting the animal. The largest cannula measures 2½ inches from bend to bend.

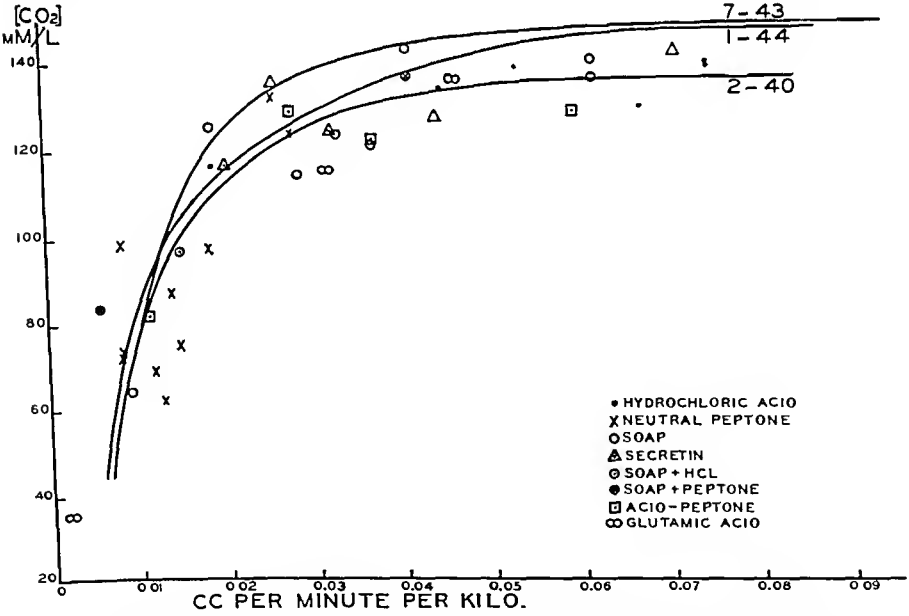

FIG. 2. CURVES SHOWING THE RELATION OF BICARBONATE CONCENTRATION (MEASURED AS TOTAL CO_2) TO THE RATE OF SECRETION OF PANCREATIC JUICE FROM THREE DOGS

"Best fitting" curves were drawn by inspection. Points are shown for only one curve, that for dog 2-40.

juice and the precautions taken we doubt if loss of CO_2 accounts for our failure to observe the low pH values frequently reported. We are, rather, inclined to believe that such values are abnormal and that pancreatic juice is normally secreted at a relatively constant pH.

DISCUSSION

In so far as our experiments parallel previous observations, our results in general confirm the earlier findings. These have been adequately discussed by the original observers.

It is evident from our results that the characteristic differences in enzyme content of pancreatic juice obtained with different secretory stimuli are not associated with corresponding differences in the bicarbonate and chloride concentrations, except in so far as each stimulus tends to produce a characteristic rate of secretion. The few discrepancies that appear in the evidence on this point are, we think, due to our inability to control adequately the rate of secretion over long periods of time. Rates of secretion of the order of 0.01 to 0.015 cc. per minute per kilo. involved collection times of 20 to 40 minutes. The pancreas in the unanesthetized dog can rarely be induced to secrete at a constant rate for so long a period of time and the crude average obtained by dividing the volume secreted by the collection time may be far from the true average rate of secretion. This difficulty, of course, applies to some extent to all of our data on rate of secretion and is probably responsible for most of the scatter observed in relating CO_2 concentration to rate of secretion.

Although we were able, within a certain range, to verify the fact that the bicarbonate concentration of pancreatic juice increases with increasing rate of secretion we find that this relationship is limited to moderate secretory rates, below about 0.05 cc./min./k. in our dogs. At higher rates of secretion the bicarbonate concentration is constant and independent of the rate. The fact that the HCl concentration of gastric juice shows a similar relation to rate of secretion (11, 6) suggests that similar mechanisms are involved in determining the concentration of HCl in the gastric juice and of bicarbonate in pancreatic juice.

At any rate much that we know about the concentration of inorganic constituents in pancreatic juice can be explained by assuming that the bicarbonate, like the HCl of gastric juice is secreted at a constant concentration in any one animal. The changes that occur at lower rates of secretion are to be expected in view of the fact that no perfect barrier exists anywhere in the body between the blood and other body fluids. If the pancreatic juice remains too long in the ducts it becomes contaminated with various blood constituents and, doubtless, loses some of its bicarbonate.

Obviously, mathematical proof of such a theory cannot be offered at present,

but it has the virtue of being simpler than some that have been proposed hitherto (10) and is in better accord with the known facts than some of the others.

The theory of Komarov, Langstroth and McRae (9) that the higher bicarbonate concentration in rapidly secreted juice is a result of increased respiratory metabolism in the gland incident to the extra work is not consistent with the constant composition of the juice at the higher rates of secretion unless the higher rates are attained without a corresponding increase in the respiratory metabolism.

The idea of continuous secretion of a neutral chloride solution is not consistent with the fact that the resting pancreas does not secrete continuously but intermittently. On the other hand such a fluid may enter the ducts by diffusion whenever secretion is present.

SUMMARY

1. Measurement of bicarbonate and chloride concentrations and pH of dogs pancreatic juice obtained with various secretory stimuli failed to reveal any true correlation between any one of these values and the stimulus used to provoke secretion.

2. Previous observations of a reciprocal relation between bicarbonate concentration and chloride concentration and of a direct relation between bicarbonate concentration and rate of secretion were confirmed.

3. It was found that the direct relation between bicarbonate concentration and rate of secretion was limited to rates below 0.05 ml. of juice per minute per kilo. weight of dog. At higher rates of secretion the bicarbonate concentration attained a constant maximum, characteristic of the animal. Maxima ranged between 135 and 148 m.M./L.

4. The analogy between conditions determining bicarbonate concentration in pancreatic juice and those determining HCl concentration in gastric juice is pointed out.

CONCLUSION

At moderate rates of secretion the concentrations of chloride and bicarbonate in dog's pancreatic juice are functions of the rate of secretion and independent of the stimulus used to provoke secretion. At higher rates they are constant and characteristic of the individual animal.

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GASTRIC EXCRETION OF SULFONAMIDES IN MAN[1]

II. Excretion of Sulfapyridine

III. Calculation of Theoretical Concentration Ratios

Henry S. Bloch, Leon Schiff, M.D., Dorothy E. Fleming, B.S., Nathan Shapiro, M.D.[2] and H. Harold Steinberg, M.D.[3]

From the Department of Internal Medicine, College of Medicine, University of Cincinnati and the Gastric Laboratory of the Cincinnati General Hospital

II. EXCRETION OF SULFAPYRIDINE

Studies on the gastric excretion of sulfadiazine and sulfathiazole in man (1) and a preliminary study of the gastric excretion of sulfapyridine (2) have been previously reported by us. The present communication deals more fully with the excretion of sulfapyridine by the human stomach. The methods used were similar to those previously described. Sulfapyridine was given intravenously as 1.0 gm. of the sodium salt dissolved in 20 cc. distilled water. The gastric excretion of the drug was observed in a group of 37 subjects, comprising 8 normals, 10 patients with duodenal ulcer, 5 with gastric ulcer, 1 with both gastric and duodenal ulcer, 5 with atrophic gastritis, and 8 with gastric cancer.

The concentration ratios of sulfadiazine and sulfathiazole were reported (1), with two exceptions, to be consistently below 1 and independent of the acidity of the gastric contents. However, the concentration ratio of sulfapyridine was usually much greater than 1 and depended on the pH of the gastric juice (fig. 1). In the presence of free hydrochloloric acid in the gastric contents (pH 1–3), the concentration ratios were usually between 4 and 8. As the pH rose above 3 the concentration ratios gradually fell until they reached values around 1 at a pH of 7 to 8. No correlation was found between the anatomical state of the stomach and the concentration ratios of sulfapyridine. The peak concentration of sulfapyridine in the gastric juice usually occurred about 60 minutes following the injection of the drug.

Five patients were given 0.5 mg. histamine subcutaneously at the time of injection of the sulfapyridine. When the histamine lowered the pH of the gastric juice without too great an increase in the rate of secretion, a definite rise in the concentration ratios occurred. Similar changes in the concentration ratios were seen in 7 patients who received 0.5 mg. histamine subcutaneously 90 minutes after the injection of sulfapyridine, i.e. after the spontaneous excretion of sulfapyridine alone had been observed.

[1] Presented in part before a meeting of the American Gastroenterological Association, June 13, 1944, Chicago, Illinois and part of a paper read before a Special Conference on Gastric Cancer, National Cancer Institute, Memorial Hospital, New York, November 11, 1944.

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[2] Fellow of the National Cancer Institute, 1940–1943; at present Captain, M.C., Army of the United States.

[3] Fellow of the National Cancer Institute, 1944–1945.

III. CALCULATION OF THEORETICAL CONCENTRATION RATIOS

Davenport (3) in 1942 published a theory of the gastric secretion of sulfonamides "based on the activities of the drugs in plasma and in gastric juice and upon their rates of diffusion through the tissues." This theory explained all the observations which Cooke, Davenport, and Goodman (4) had made on dogs. While the results obtained by these authors are generally in good agreement with our data in humans, Cooke, Davenport, and Goodman did not report a change of the concentration ratio with change in pH. This is not surprising because their studies were performed on normal pouch dogs which are known to have a gastric secretion with a consistently low pH following the injection of histamine.

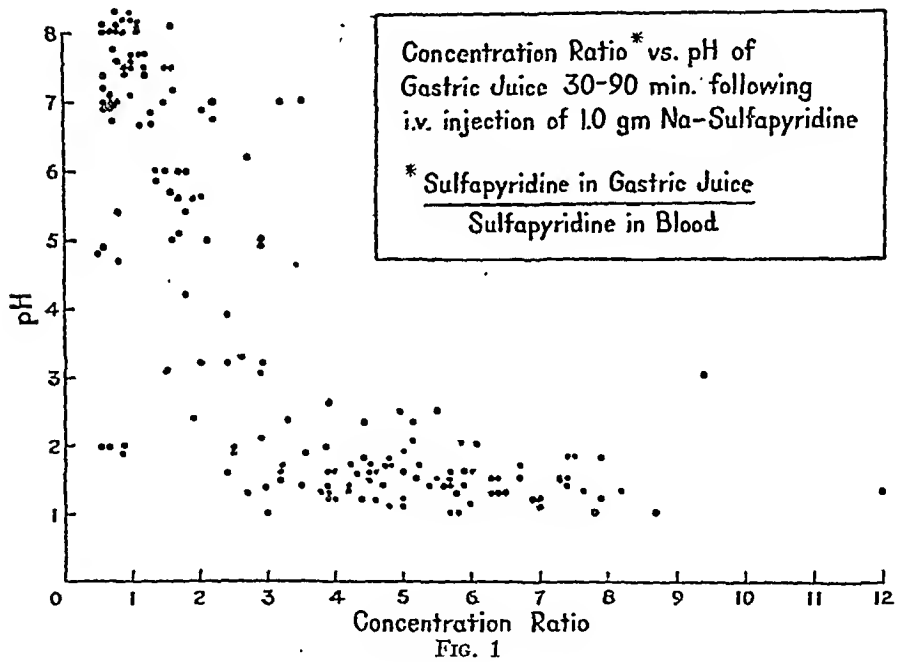

FIG. 1

We have calculated the theoretical concentration ratios for sulfapyridine, sulfathiazole, and sulfadiazine over a pH range of 1 to 8 for gastric juice, postulating a simple diffusion mechanism for the gastric secretion of these drugs, in accordance with Davenport's concept. The calculation was carried out as follows:

Assume the existence of two aqueous well-buffered solutions of pH = P and pH = G respectively, separated by a membrane which is freely permeable to the sulfonamide in the undissociated form. Let the total concentration of the sulfonamide and the concentration of any of its forms in either solution be much lower than saturation. The total concentration of the sulfonamide in either solution will be equal to the sum of the concentrations of the undissociated, basic, and acid forms (1).

$$[T] = [U] + [B\cdot] + [A'] \tag{1}$$

$[B\cdot]$ and $[A']$ can be expressed in terms of $[H\cdot]$, K_a, K_b,

$$[B\cdot] = \frac{K_b}{10^{-14}}[H\cdot][U] \tag{2}$$

$$[A'] = \frac{K_a}{[H\cdot]}[U] \tag{3}$$

Substituting the values for $[B\cdot]$ and $[A']$ obtained from (2) and (3) in (1), and separating [U], (4) is obtained.

$$[T] = [U]\left\{1 + \frac{K_b}{10^{-14}}[H\cdot] + \frac{K_a}{[H\cdot]}\right\} \tag{4}$$

The concentration ratio between the solution with pH = G and the one with pH = P then becomes (5).

$$R = \frac{[T]_G}{[T]_P} = \frac{[U]_G\left\{1 + \frac{K_b}{10^{-14}}[H\cdot]_G + \frac{K_a}{[H\cdot]_G}\right\}}{[U]_P\left\{1 + \frac{K_b}{10^{-14}}[H\cdot]_P + \frac{K_a}{[H\cdot]_P}\right\}} \tag{5}$$

Assume:

$$[U]_G = [U]_P \tag{6}$$

Then:

$$R = \frac{1 + \frac{K_b}{10^{-14}}[H\cdot]_G + \frac{K_a}{[H\cdot]_G}}{1 + \frac{K_b}{10^{-14}}[H\cdot]_P + \frac{K_a}{[H\cdot]_P}} \tag{7}$$

The theoretical concentration ratios of sulfapyridine, sulfadiazine, and sulfathiazole, as obtained from equation (7) for $[H\cdot]_G$ corresponding to pH values from 1 to 8 for gastric juice and for $[H\cdot]_P$ corresponding to the pH of plasma and tissue fluids (pH = 7.4), and using values of K_a and K_b for the sulfonamides as determined by Bell and Roblin (5),[5] are plotted against the pH of gastric juice in figure 2.

[4] Identity of symbols used in equations (1) to (7):
[T] = total concentration of sulfonamide
[U] = concentration of undissociated sulfonamide
[B·] = concentration of basic form of sulfonamide
[A'] = concentration of acid form of sulfonamide
[H·] = concentration of hydrogen ion
K_a = acid dissociation constant of sulfonamide
K_b = base dissociation constant of sulfonamide
[ ]$_G$ = concentration in solution G
[ ]$_P$ = concentration in solution P
10^{-14} is the dissociation constant of H_2O

	K_a	K_b
[5] Sulfapyridine	3.7×10^{-9}	3.8×10^{-12}
Sulfadiazine	3.3×10^{-7}	1.0×10^{-12}
Sulfathiazole	7.6×10^{-8}	2.3×10^{-12}

On comparing the curve for sulfapyridine with the experimental data obtained for this drug (fig. 1) it becomes apparent that the experimentally determined concentration ratios of 4 to 10 at pH 1 to 2 are easily accounted for. The same is true for the concentration ratios at pH 7 to 8. However, at the intermediate pH range of 2 to 7 the experimentally obtained concentration ratios are appreciably larger than the theoretical values. This difference can be readily explained if one accepts the theory that gastric juice is a mixture of at least two secretions, one originating in the parietal cells with a pH of about 1, and the second originating from the remainder of the gastric mucosa with a pH of 7 to 8. The intermediate pH values and the corresponding concentration ratios are produced by mixture of the two secretions.

In a previous study we found the concentration ratio of sulfadiazine in men to be generally around 0.5 and independent of the pH. Postulating again, that

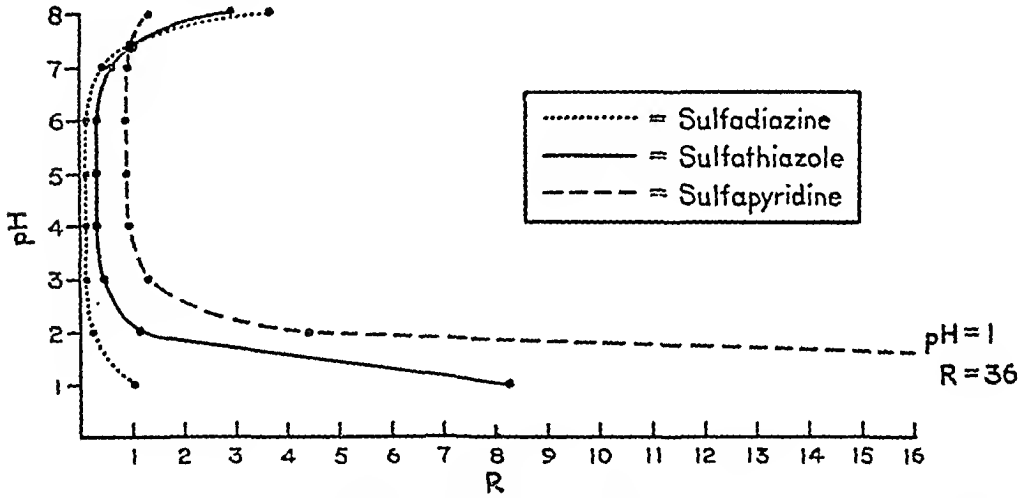

FIG. 2. THEORETICAL CONCENTRATION RATIOS OF SULFAPYRIDIEN, SULFATHIAZOLE AND SULFADIAZINE AT DIFFERENT pH VALUES

gastric juice is a mixture of at least two different secretions with pH of about 1, and 7 to 8 respectively, one would expect a concentration ratio of about 1 from the calculated value, independent of the pH values of the gastric juice (the theoretical concentration ratio of sulfadiazine is about 1 for gastric secretion at pH of about 1 as well as at pH 7.4). The fact that the experimentally determined concentration ratios were generally found to be around 0.5 may be attributed to the low diffusion constant of sulfadiazine (ka = 0.252 (Davenport)).

For sulfathiazole, the calculated ratios fell between the concentration ratios of sulfapyridine and sulfadizine. Actually the concentration ratios found with this drug in both humans and dogs were appreciably lower (about 0.2) (1, 4). This again may be attributed to the low diffusion constant of sulfathiazole (ka = 0.175 (Davenport)) which is considerably smaller than the one of sulfapyridine (ka = 2.7 (Davenport)) or sulfadiazine.

ACKNOWLEDGMENTS

We wish to thank Drs. M. B. Visscher and N. Lifson of the University of Minnesota for their valuable suggestions in the theoretical treatment of our data. The sodium sulfapyridine was furnished by the Lederle Laboratories through the courtesy of Dr. Benjamin W. Carey.

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GASTROTOMY FOR TRICHOBEZOAR

Case Report

Jacob Sarnoff, M.D. and Stanley J. Sarnoff, M.D.

Brooklyn, New York[1]

INTRODUCTION

In the sixteenth century a description of the various types of animal bezoars and the therapeutic powers ascribed to them, was published by Imad-ul-Din (1). Baudamant, in 1777 (2), was the first to report a trichobezoar in the human, and Ramsbottom and Barclay, in 1913 (3), were among the first to make the diagnosis by roentgen examination. De Bakey and Ochsner collected 172 cases and thoroughly reviewed the literature in 1938 (4). Miller and Kert (5) contributed three additional cases in 1944.

Trichobezoar, or hair ball, is to be distinguished from phytobezoar or foreign body composed of miscellaneous vegetable material such as stems, leaves, persimmon seeds, etc. Combinations of hair and vegetable material are designated as trichophytobezoars. In addition, the ingestion of shellac and liquid latex has been reported as giving rise to large gastric concretions.

Meilchen's experiments on hair feeding (6) in the rat and rabbit demonstrated that the nature of the ingested foreign body is not solely responsible for the formation of the gastric concretion, but that the accompanying food plays a role in determining whether or not concretion will occur.

That a bezoar may not limit itself solely to causing symptoms of discomfort because of its presence in the stomach is indicated by the case reported by Allen (7). Accompanying this bezoar, a large ulcer was observed on the lesser curvature of the stomach. It would be difficult, however, to establish a causal relationship in any given case.

Sex is apparently an important factor, since the ratio of females to males is approximately 11 to 1 in trichobezoar and 3 to 1 in phytobezoar. The largest number of trichobezoars was found in the second decade of life while phytobezoars were most frequently encountered in the sixth decade.

The percentage of individuals with trichobezoar who show some obvious mental abnormality is somewhat lower than would be anticipated, being only 14%. An interesting discussion of this aspect of the problem is to be found in the report of Miller and Kert.

In view of the size of some of the intragastric concretions, the clinical manifestations of bezoars are remarkably mild, unless there is an accompanying ulcer or obstruction or perforation occurs. Although severe pain has been

[1] 1406 Albemarle Road.

recorded, it is far more usual for these patients to relate a history of moderate epigastric discomfort, more pronounced after eating. Despite the fact that after removal, the bezoars almost always have a foul odor, unpleasant breath is not usually complained of. The larger concretions are palpable in the epigastrium and crepitation is rarely elicited. Obvious trichophagia is observed in most patients.

Buckstein (8) has established the roentgenologic criteria for the diagnosis of bezoar and it is on this basis that the clinical diagnosis is usually made. 1) The shadow of the mass is centrally located, so that the contours of the stomach are unaffected and exhibit normal peristalsis. 2) The intragastric position of the mass may be altered manually under fluoroscopic control. 3) If the mass is large, it may invaginate the air bubble of the stomach in the erect position and stand out in clear relief. The roentgen findings of the case about to be reported conformed to these criteria.

CASE REPORT

At the age of six months, an otherwise normal infant had acquired the habit of picking the wool from her blankets and swallowing it. This was successfully prevented by covering the blankets with muslin. However, when the infant was one year of age, she was observed to be removing some of her own hair, rolling it into a ball and swallowing it. At eighteen months of age she vomited a trichobezoar the size of a hen's egg, and at this time her hair was trimmed short, but was allowed to grow long during the following year. Occasional attacks of abdominal pain were attributed to gastro-intestinal upsets. Three months before operation, hair was noticed in the child's stool. Two weeks before operation the child complained of mild abdominal pain, and the history of trichophagia, together with the palpable epigastric mass, prompted the family physician[2] to perform roentgenologic studies (fig. 1). Buckstein's criteria were observed to be present. The size of the bezoar precluded any attempt at removal by emesis or gastroscopic manipulation and operation was advised.

Spinal anesthesia, using 40 mgm. of procaine hydrochloride, provided satisfactory upper abdominal relaxation. A left rectus, supraumbilical incision was made and a firm, oblong, freely movable mass, was palpated through the stomach wall. A vertical incision permitted the delivery of the trichobezoar.

The trichobezoar was approximately the shape of the body of a violin. It was 11 x 7 x 4 centimeters, was greenish-black in color, had a foul odor and had the consistency of thick felt. The individual groups of hair fibers were closely intertwined and were teased apart with difficulty (fig. 2). A lamellated appearance was observed on cross-section.

When a bezoar is not too large, it may be possible to remove it by emesis, as was demonstrated by the spontaneous regurgitation of this patient's first bezoar

[2] The authors wish to express their gratitude to Dr. Irwin M. Stillman.

FIG 1 X-RAY OF THE TRICHOBEZOAR

The mass is to the left of the bodies of the vertebra extending from above the tenth rib to below the twelfth

FIG 2 THE TRICHOBEZOAR

When the mass attains the size of a tangerine, however, gastrotomy is indicated.

Because of the rarity of this condition and the relatively small number of physicians who have an opportunity to see this type of case, motion pictures in color were taken of the pre-operative condition, the roentgenological studies, the operative procedure, the specimen, and the end result. These films are available to the medical profession (9).

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BISMUTH SUBNITRATE POISONING WITH METHEMOGLOBINEMIA

A Report of a Case in a Diabetic[1]

George E. Miller, M.D.
Buffalo General Hospital, Buffalo, New York

INTRODUCTION

Toxic reactions to bismuth subnitrate are rare. They appear clinically in two forms: (1) bluish pigmentation of the gum margins and buccal mucosa, metallic taste, soft and bleeding gums, and ulcerative stomatitis; (2) dyspnea, 'cyanosis', methemoglobinemia and circulatory collapse.

THE CASE REPORT

The following case is presented as an example of the latter type of poisoning:

Mrs. R. S., a white housewife aged 57, first came under our care in 1936 when classical symptoms and signs of diabetes mellitus appeared. The diabetes was controlled by diet and 30 units of regular insulin daily and on this regimen she remained in fair health until 1938, at which time she was readmitted with severe diabetic acidosis. Since that time she has had ten readmissions because of acidosis; five of these have been in the past year. On each occasion the acidosis has been precipitated by an acute gastro-intestinal upset consisting of diarrhea, abdominal pain, nausea and vomiting. Between attacks the diabetes has been acceptably controlled on a diet, to which she has adhered as well as the average diabetic, and about 60 units of insulin.

During an admission in July 1942, mild signs of cardiac decompensation appeared. An electrocardiogram revealed a left bundle branch block. Very slight limitation of activity has resulted in complete relief of these cardiac signs.

On June 1, 1944, after two months of freedom from diarrhea, she again developed a typical attack for which she was given bismuth subnitrate, 2 grams every six hours, to a total dose of about 12 grams. During the night, 48 hours after the onset, she experienced what she described as a crushing and burning pain behind the sternum and in the epigastrium which became progressively more severe. Prior to her admission to the hospital the following morning she received morphine sulfate 0.015 gm. which brought her some relief. On admission she presented a rather alarming clinical picture of cyanosis of the lips and nail beds, shallow labored respirations and partial stupor. Her temperature was 98° F. The blood pressure was 68 systolic and 50 diastolic. The pulse rate was 100, of poor quality. The heart tones were inaudible. There was evidence of moderate dehydration. No abnormalities were detected in the lungs or the abdomen.

Laboratory findings. Red blood cells were 4,500,000 per cmm. and hemoglobin was

[1] From the Medical Clinic of the Buffalo General Hospital and the School of Medicine of the University of Buffalo.

13 gms. per 100 cc. White blood cells numbered 12,000 per cmm., and the differential count showed a marked left shift. The urine showed a 4 plus sugar and a 1 plus acetone. The blood sugar was 330 mg. per 100 cc. Electrocardiogram showed no change when compared with the one taken two years earlier.

Course. The use of an oxygen solarium slightly eased the dyspnea and substernal pain, but the cyanosis was not relieved. She was given normal saline solution subcutaneously, strychnine sulfate 0.001 gm., and crystalline insulin 20 units. The insulin was repeated in 15 unit doses every six hours. During the next 12 hours she became progressively more stuporous and was incontinent of urine and feces. The following morning there was no essential change in her clinical state. At this time her blood sugar was 222 mg. per 100 cc.; blood urea nitrogen 49 mg. per 100 cc.; CO_2 combining power of the plasma, 15 volumes per cent. It was noted that the blood had a peculiar chocolate hue, and for that reason methemoglobinemia was suspected. Spectroscopic analysis of the blood revealed the methemoglobin level to be approximately 70 per cent. During this day she was given an intravenous clysis of 5 per cent glucose in normal saline, covered by insulin, and a transfusion of 500 cc. of whole blood. Her respirations became less labored and the 'cyanosis' became noticeably less. Her blood pressure rose to 100 mm systolic and 60 mm diastolic. She received 65 units of crystalline insulin during this 24 hour period.

The next day, the 'cyanosis' had completely disappeared, the respirations had become normal, and it was possible to remove her from the oxygen solarium without ill effect. Blood glucose at this time was 174 mg. per 100 cc. and CO_2 combining power, 27 volumes per cent. (It had been our previous experience with this patient that during recovery from bouts of acidosis her CO_2 combining power rose very slowly and that the blood urea nitrogen was slow to be reduced to her usual level, probably because of the existence of an associated kidney lesion.) The blood now showed only a trace of methemoglobin. Vomiting and diarrhea had ceased. Her blood pressure had returned to normal. There was no recurrence of the substernal pain.

The remainder of her hospital stay was uneventful, and she was discharged on June 12 with the diabetes well controlled.

It should be noted that this patient had taken bismuth subnitrate on several previous occasions, for the control of diarrhea, without any toxic manifestations.

COMMENT

Methemoglobin is a brown pigment which is formed by the oxidation of reduced hemoglobin, a reaction which involves a change in the iron of the heme radical from the ferrous (Fe++) to the ferric (Fe+++) form. This is distinct from oxyhemoglobin which is an oxygenation product of reduced hemoglobin, a reaction in which there is no change of iron valence but simply an addition of molecular oxygen to the ferrous heme radical. Methemoglobin does not dissociate into oxygen and hemoglobin under reduced oxygen pressure.

Methemoglobin will form slowly in standing blood, but the reaction may be

hastened by certain oxidizing agents. In vivo both oxidizing and certain reducing agents (which act as oxygen carriers) will produce methemoglobinemia. These substances include: acetanilide, aminophenols, anilin, antipyrin, chlorates, ferricyanides, nitrites, nitrobenzene, phenacetin, sulfanilamide and others. Methemoglobin may also be produced in vitro by growing cultures of certain bacteria including the pneumococcus (10) and intestinal putrefactive organisms.

The striking physical characteristics of methemoglobin are its distinctive chocolate brown color and the spectroscopic absorption band whose center lies at 6340 Angstroms.

Clinically methemoglobinemia is characterized by 'cyanosis' and dyspnea. The 'cyanosis' occurs when methemoglobin level reaches three grams per 100 cc. of whole blood. This 'cyanosis' is of a deeper shade than that produced by excessive amounts of reduced hemoglobin. Most cases do not progress to the higher methemoglobin levels where dyspnea becomes apparent. Because of the inability of methemoglobin to form an unstable linkage with oxygen, the therapeutic administration of oxygen does not lessen the degree of anoxemia to any great extent and will not relieve the 'cyanosis'.

Five cases of methemoglobinemia following the administration of bismuth subnitrate have been found in the literature:

Bennecke and Hoffman (1) reported the first case of methemoglobinemia due to bismuth subnitrate in a child three weeks old who was given three grams of the drug in 100 cc. of buttermilk, by gavage, as a contrast media for roentgen investigation of a pyloric stenosis. Twelve hours after the administration of the bismuth subnitrate the child developed a progressive 'cyanosis' with peripheral circulatory failure and death. Methemoglobin was present in the blood at post-mortem and no other explanation for death was found.

The second case, reported by Boehme (2) occurred in a child one and one-half years old with rickets and marasmus. For x-ray study a few grams of bismuth subnitrate was instilled into the stomach by gavage, later washed out, and no toxic effects were noted. Several days later several grams were instilled into the rectum and again washed out. Three hours later the patient developed abdominal pain, a progressive 'cyanosis', peripheral circulatory failure and death. At postmortem examination a methemoglobinemia and pyloric stenosis were found. The rectum contained a large amount of bismuth subnitrate.

The third case (3) occurred in a forty-four year old man who had four tablespoonsful of bismuth subnitrate in two litres of water instilled into the rectum as a contrast media. Following roentgenography the substance was expelled. Twelve hours later he developed a progressive 'cyanosis', dyspnea and pe-

ripheral circulatory failure with death. The blood at the time of death was chocolate colored and methemoglobin was present.

The fourth report (4) concerned a male infant, one month old, with persistent diarrhea, vomiting, fever. Shortly after he was first seen he developed a bilateral otitis media which was successfully drained. After twelve days of diet treatment without response bismuth subnitrate, in dose of 0.6 Gm. every two hours, was instituted. Twenty-four hours later a mild degree of 'cyanosis' was first noted. Forty-eight hours after this (total dose of bismuth subnitrate 13 gm.) the 'cyanosis' had deepened, dyspnea had appeared, and the temperature rose to 107.6°F. The bismuth subnitrate was stopped at this time, and the infant placed in an oxygen tent. In spite of supportive therapy the course was steadily downward with increasing respiratory difficulty and sixty hours after the bismuth was started, the child was dead. At post-mortem a bilateral otitis media and bronchopneumonia were found. The blood (four hours after death) was chocolate colored and spectroscopically revealed a large quantity of methemoglobin.

The most recent report (5) is of a twenty-one year old white female, a diagnosed case of chronic non-specific ulcerative colitis. Without the knowledge of her physician she had taken four grams of bismuth subnitrate almost daily for twenty-one months. Her presenting complaint was blueness of the lips and fingertips which had been present intermittently for the month before she was first seen. Physical examination revealed nothing abnormal other than the 'cyanosis' of lips and skin. Spectroscopic analysis of the blood revealed a methemoglobin level of five grams in each one hundred cc. of whole blood. The bismuth subnitrate was stopped and within forty-eight hours the cyanosis had disappeared, and the blood showed only one gram of methemoglobin in each one hundred cc.

In the production of methemoglobinemia by bismuth subnitrate the bismuth plays no part: the entire reaction is produced by a conversion of nitrate to nitrite in the intestinal tract, the absorption of nitrite into the blood stream with the formation of methemoglobin. The conversion of nitrate to nitrite in the enteric canal has been amply demonstrated experimentally, and this fact has been used clinically in the past when bismuth subnitrate was used as a therapeutic agent in essential hypertension (6). Following its administration, small quantities of nitrite may be detected in the urine.

Other nitrates taken by mouth are also capable of producing methemoglobinemia. Seven cases of methemoglobinemia resulting from the administration of ammonium nitrate as a diuretic have been reported (7, 8, 9). In these cases (all with massive edema) the drug was given in total dosage of twenty-four to four hundred fifty-six grams before the signs appeared. In only one of

these patients was there any demonstrated abnormality of gastrointestinal function (this a poorly functioning gastro-enterostomy). Two of the patients had cirrhosis of the liver.

In the case reported here the major gastrointestinal abnormality was a chronic recurrent diarrhea of undetermined etiology. Diarrhea was present in two of the other patients reported in the literature. In the cases of methemoglobinemia produced by ammonium nitrate, "intestinal stasis" was more frequently found and implicated as a contributing factor.

No satisfactory explanation has yet been offered for the appearance of a nitrite methemoglobinemia in these patients, and at the moment there seems no common denominator to these rare reactions. Whatever the explanation, the possibility of a serious, even fatal, complication of the use of this common drug should be recognized and the indications carefully considered before it is prescribed. It should be remembered that bismuth subcarbonate, a drug of equal value in the treatment of diarrhea, is not attended by the risk of methemoglobinemia.

Acknowledgment. To Dr. B. D. Bowen an expression of appreciation for his cooperation in making the presentation of this case report possible.

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EDITORIALS

EPIDEMIC TRANSIENT VOMITING AND DIARRHEA OF UNKNOWN ORIGIN

In a recent article (Jour. A. M. A., **127**, 1–6, 1945) Reimann, Hodges and Price have discussed that strange combination of vomiting and diarrhea that sometimes sweeps suddenly through a dormitory or college or barracks, knocking out for a day or two perhaps 20 per cent of the personnel. Although for a few hours the disease can be most distressing, the attack is usually of such short duration that it is not deemed of much importance and therefore few physicians have concerned themselves much with the problem. Curiously, the epidemics tend to come in the autumn months. So far no causative virus or Bacterium has been isolated but it would seem that the cause must be infectious in nature and airborne because many persons in a community tend to fall ill at the same time.

Some writers have assumed that the trouble must be due to a gastro-enteritis, while others have been impressed with features which suggest that the mechanism which empties the bowel violently in both directions is a nervous one. Our own impression from observing and experiencing attacks of the disease was that the mechanism was most probably a nervous one. The striking feature of the spells observed was the sudden onset with simultaneous projectile vomiting and uncontrollable diarrhea. The intestinal contents ran out of the rectum easily without any cramps; the abdomen was soft and not tender, and there was no soreness of the bowel. There was practically no rise in temperature or pulse rate. The intestinal contents were not irritant to the anal ring. The attack was over in a few hours, and after that there were only the amounts of fatigue and mental hebetude that one would expect after so strenuous a session. The impression gained was that if the patient had had a gastro-enteritis severe enough to produce so violent an emptying of the digestive tract, there should have been present the well-known syndrome of fever, toxemia, and a tense sore abdomen. Furthermore, if the bowel wall had been badly inflamed and the lumen full of bacteria, recovery could hardly have taken place so suddenly without there being left much intestinal soreness. If, also, the disease were associated with an infectious process in the bowel, one would expect an epidemic to leave in its wake a number of cases of chronic diarrhea, and this does not appear to be the case.

WALTER C. ALVAREZ.

ESSENTIAL FACTS ABOUT MIGRAINE

It is unfortunate that one of the commonest diseases seen each week by the gastroenterologist is one about which he was taught little if anything at college, and about which he can find little in the literature. Because of this and his lack of any clear idea as to the etiology of the disease, when a patient comes complaining of sick headache or "toxic vomiting", the doctor often fails to make the right diagnosis and almost always today agrees with the patient that a most thorough overhauling should be made; one which will almost certainly reveal the *cause* of the trouble, probably in the abdomen. In carrying out the exhaustive examination the doctor usually wastes the woman's money and his time because he does not find anything that is helpful. As Mollendorf pointed out back in 1867, migraine is an entity—a peculiarity of the nervous system—and the "cause" is to be found only in the patient's heredity. The trouble is not in the digestive tract but up in the brain, and the stomach is upset just as it is in seasickness—by a storm which goes down the vagus or the splanchnic nerves. Things like menstruation, eyestrain, constipation or food allergy are just nagging irritants that can help to "spring the trap."

Evidently then, one cannot hope to *cure* the patient by the surgical removal of any part of the digestive tract. The migrainous temperament will remain, and recent studies have shown that this temperament is the big thing in causing the headaches and the nervous storms.

The essential fact about migrainous women (men seldom have the disease in a disabling form) is that they are all nervous, tense, intelligent, highly sensitive and reactive, socially attractive, quick, conscientious and painstaking, with a marked tendency to fatigue easily and to wilt suddenly.

Even when a woman of this type and with the migrainous inheritance is relieved of her headaches she usually continues to suffer because she can never stand much strain or excitement. Furthermore, most migrainous women have bad days when they are depressed, half-alive and miserable, much as if they had a spell without the headache and vomiting.

Because many migrainous women fail to give the essential history, and even try to conceal their handicap, the physician who would make the diagnosis must often recognize at a glance the trim, attractive, wide-awake, and quick-witted type of woman who has sick headaches. Then if he finds that she gets her headaches or spells of vomiting or "intoxication" or "duodenal ileus" or abdominal pain *in a typically migrainous way*—after she has gotten tense or excited or tired—the doctor can be pretty sure that he is dealing with migraine. If he depends only on such facts as that the headache is unilateral or preceded by a scotoma or followed by vomiting he will often go wrong because there are too many cases in which the syndrome is atypical. A helpful point is that years

before, the girl used to be sent home from school with bilious vomiting, or that during pregnancies she was free from the headaches. In many cases the patient has one or two types of fatigue or menstrual headache besides the bad bilious one, and then the several parts of the story must be unscrambled skillfully before the clinical picture can emerge clearly. An intramuscular injection of gynergen (ergotamine tartrate), given at the start of an attack, can often be used diagnostically. If it aborts the attack, the disease is almost certainly migraine.

As intimated already, the examination rarely shows anything helpful. An important point, not generally recognized even by authorities, is that sometimes the migrainous person is plagued by an added inheritance of constitutional inadequacy, psychopathy, hypertension, allergy, epilepsy, hyperthyroidism or poor pelvic organs. Such an extra handicap is likely to cause the attacks to come more frequently and to be more severe.

Because of her frequent illnesses, her undependability, and her need for good care and perhaps help in the care of the home, the migrainous woman must get an angel for a husband, and commonly she does. But not infrequently she is unhappy with him because he is not enough of a lover and she is so romantic she wishes she had done better. This sort of unhappiness, together with thoughts of divorce, causes the attacks to come more frequently.

There are probably few cases in which the migrainous woman does not need psychiatric help with her life problems. This is so true that the wise physician will spend little time on probably futile examinations and as much time as he can spare on almost certainly helpful advice in regard to living and adjusting and acquiescing to what can't be helped.

WALTER C. ALVAREZ.

COMMENT

THE INTERDIGESTIVE SECRETION OF HYDROCHLORIC ACID

This comment has been excited by the discussion which followed the report of Dr. L. R. Dragstedt in the December issue of Gastroenterology. In patients with peptic ulcer he studied the "night" or continuous secretion before and after supradiaphragmatic bilateral vagotomy. In his discussion with Dr. Sandweiss, Dr. Dragstedt pointed out that "we need a great deal more data on this factor of continuous secretion, independent of stimulation of the gastric glands by histamine, alcohol, or food" in man. We should like to emphasize that this is particularly true of patients who have been vagotomized above the diaphragm.

Does the stomach secrete hydrochloric acid in the absence of the same stimuli (food) which are responsible for acid secretion in response to a meal? When the contents of the stomach are continuously drained away by means of a stomach tube the secretions recovered from the fasting stomach in man and the dog almost always contain free HCl. Bloomfield (1) has applied the term *basal anacidity* to the condition in which there is an absence of free HCl in the fasting secretions of a person whose gastric glands are capable of responding to histamine stimulation with acid formation. According to Bloomfield, basal anacidity is a rare occurrence. The amount and acidity of the interdigestive secretion vary from person to person and from time to time in any one person. It is present in variable amounts throughout a fast of forty days (2).

When a pouch has been fashioned from the stomach of a dog interdigestive secretion of acid is still noted. This is true for all types of pouches, vagally innervated and vagally denervated pouches of the entire stomach, subcutaneously autotransplanted pouches (devoid of all original extrinsic nerve and vascular supply), and all other types of experimental pouches which have been observed. Occasionally a gastric pouch will exhibit a basal anacidity, that is it will secrete only in response to a meal or pharmacological stimulation. Such pouches, as a rule in our experience, are relatively refractory and secrete poorly even when strong stimulation is employed.

Thus, it may be categorically stated that the normal human and canine stomach secretes HCl during the interdigestive period. Unless one recognizes that the empty stomach does secrete acid at periods, one will erroneously interpret the occurrence of normal periodic interdigestive secretion after the introduction of an experimental procedure as evidence of stimulation. Therefore, in experimental work on man and animal the interdigestive secretion should be collected for a period before any procedure is introduced, and the fact should be kept in mind that a small increase or decrease may be spontaneous.

Pavlov (3) believed that the gastric glands do not secrete acid during the interdigestive period and that if acid is present it is due to the thought or odor of food. Essentially the same viewpoint is taken by Babkin (4) who however believes that other factors such as swallowing of saliva or regurgitation of duodenal juices, mechanical stimulation of the mucosa of the pyloric part of the stomach, food masses in the intestine, etc., might also contribute to interdigestive secretion. Psychic influences and the other factors mentioned can and probably do contribute to interdigestive secretion. However none of these factors can explain the occurrence of interdigestive secretion in the subcutaneously transplanted pouch. According to Babkin (4) vagal denervation of the gastric glands induces a continuous "paralytic" secretion of acid gastric juice. Babkin therefore considers the interdigestive secretion of HCl in vagally denervated pouches to be due to an abnormal mechanism of unknown nature, hence the designation "paralytic" secretion. The Pavlov-Babkin school thus holds that the interdigestive secretion noted in the vagally innervated stomach is due mainly to conditional reflexes whereas the interdigestive secretion noted after vagal denervation is due to an abnormal mechanism, "paralytic" secretion. This interpretation is based on the belief that after vagal denervation the stomach secretes HCl *continuously*, in contrast to the *intermittent* or periodic interdigestive secretion of HCl noted before vagotomy. This is the crux of the misunderstanding. In our laboratory (where probably more vagally denervated stomach preparations have been observed than in any other laboratory in the world), it has been a consistent observation that *healthy dogs with vagally denervated gastric pouches secrete hydrochloric acid intermittently and not continuously.*

The "paralytic" or continuous secretion of HCl after transection of the vagi has not been noted by us after the effects of the trauma of the operation have disappeared (7 to 21 days). It is true that continuous secretion of HCl sometimes occurs in gastric pouch dogs and we too consider this to be an abnormal state. But it occurs with no greater frequency and lasts no longer in dogs with vagally denervated pouches than in those with vagally innervated pouches. This abnormal continuous secretion of hydrochloric acid frequently occurs for several days after an operation has been performed upon a dog. It also occurs when lesions such as erosions of the skin about the stoma of a pouch are present, and in other conditions such as lactation, and in the Mann-Williamson dog.

In both uncomplicated vagally innervated and vagally denervated pouches the interdigestive secretion of HCl is intermittent and is always small in amount. The periods during which no acid is being secreted may last from one-half to three hours. During the period of secretion, the average pouch of the entire stomach (vagally denervated) may produce from 10 to 20 mg. of HCl per hour. When hydrochloric acid is not being secreted the pH of the gastric

secretion has been observed to rise as high as 7.5. There is no lack of agreement concerning the fact that the secretion of the non-parietal elements of the gastric juice is continuous in character in man and the dog.

The cause of the intermittent secretion of HCl during the interdigestive period is unknown. It is at least in part independent of vagal impulses and therefore of conditional reflexes.

The only opportunity to study the interdigestive secretion in the vagotomized stomach of man has been in cases of ulcer where abnormal mechanisms of gastric stimulation may be operating so that conclusions concerning the normal cannot be drawn. Sometime after the ulcer of the vagotomized patient has healed, it would be obviously important to collect the gastric contents at 10 or 20 minute intervals after a period of 18 to 24 hours of fasting. This has not been done by Dr. Dragstedt. If a periodic secretion of acid occurred, it could not then be accounted for as due to the thought or odor of food. If the presence of a tube stimulates secretion, it would be odd for it to do so only periodically. Further, the autotransplanted pouch in the dog may occasionally manifest a periodic secretion of acid in the absence of a tube.

Knowledge of this kind is important because the study of interdigestive secretion is of interest in relation to the pathogenesis of peptic ulcer. The interdigestive secretion of HCl in peptic ulcer patients is usually substantially above the normal average (5). This exposure of the gastro-duodenal mucosa to excessive secretions in the absence of the protective action of food may be an important factor in ulcerogenesis.

The only purpose of this comment is to delineate the known and unknown concerning interdigestive secretion in man as a basis for further investigation.

M. I. Grossman.
A. C. Ivy.

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ABSTRACTS OF CURRENT LITERATURE

FRANKLIN HOLLANDER

Associate Editor in Charge of Abstracts
Mount Sinai Hospital, New York City

STOMACH

RENSHAW, R. J. F. Gastroscopy. Cleveland Clinic Quart., 11: 93 (Oct.) 1944.

The diagnostic study of many patients cannot be considered adequate and complete without gastroscopy. Gastroscopy is an office procedure. Contraindications for examination are chiefly diseases of the esophagus and mediastinum. Its limitations are few, the main one being the "blind areas" of the stomach which vary in size. The procedure is indicated: (1) in further study of patients with negative roentgenologic findings in whom gastric disease is suspected; (2) for classification of many cases with indeterminate, suspicious, or inconclusive roentgenologic findings; and (3) for elucidation of certain obscure conditions such as unexplained gross hemorrhage and gastrointestinal allergy. Gastroscopy in combination with roentgenoscopy and study of gastric content removed by fractional method of gastric analysis has made the diagnosis of organic disease of the stomach comparatively simple.

IRVING WOLMAN.

MEYER, K. A., AND STEIGMANN, F. The surgical treatment of corrosive gastritis. Surg. Gyn. Obs., 79: 306 (Sept.) 1944.

Corrosive gastritis is a pathological condition of the stomach following the ingestion of some corrosive substance, and it usually requires surgical intervention for its relief. Not as infrequent as formerly thought, this condition occurs quite often among charity patients. The sequelae of ingestion of a corrosive substance may occur anywhere from several days to several months later, and it is quite common that the patient will fail to recall the time of the ingestion. The value of securing a good history is stressed. All patients seen required surgical intervention for relief of gastric obstruction. Gastroenterostomy rather than resection is recommended. The dangers of secondary gastrojejunostomy ulceration are minimal since there is no free acidity present in these stomachs. Patients must be prepared carefully and for a long time, if necessary by jejunostomy feedings, for the final operation on the stomach. In some cases with very small fundic pouches, "sham feedings" are given to distend this portion sufficiently to permit the gastroenterostomy.

FRANCIS D. MURPHY.

BLUM, S. D. Peptic ulcer of the greater curvature of the stomach. Am. J. Roent. Rad. Therapy, 52: 291 (Sept.) 1944.

Benign ulcers of the greater curvature of the stomach are rare. Blum reported a case in which the X-ray revealed a large ulcer niche on the greater curvature of the antrum of the stomach, which proved to be benign. In this case the mucosal folds were prominent and converged toward the ulcer. There was an absence of the meniscus sign. The author pointed out that only 15 proven cases of benign peptic ulcer of the greater curvature of the stomach have been found in the literature.

MAURICE FELDMAN.

BOWEL

O'DONOVAN, E. J., AND MURPHY, F. D. Extrarenal uremia: report of two cases due to pyloric obstruction. Ann. Int. Med., 21: 662 (Oct.) 1944.

Two cases of extra-renal uremia are described, both due to pyloric obstruction. The one resulted from fibrous pyloric stenosis following a previous peptic ulcer, and terminated in death. The other resulted from dense adhesions about the pylorus, liver, and duodenum following a subdiaphragmatic abscess from a perforated peptic ulcer 10 month before. The latter patient recovered, following posterior gastro-enterostomy.

Prolonged dehydration from the upper intestinal obstruction produced the extrarenal azotemia, in consequence of salt loss and the resultant diminution of extracellular fluid. Hemoconcentration ensues with a corresponding rise of colloid osmotic pressure, which in turn results in a diminution of renal filtration pressure and blood flow to the glomeruli. Hypochloremia alone is not the cause. Treatment is outlined, consisting of large amounts of fluids (up to 7000 cc. daily on occasion), blood transfusion, electrolytes (depending on the degree of acidosis or alkalosis), anti-spasmodics, and frequent small feedings. Surgical relief of the obstruction should be done where indicated.

FRANK G. VAL DEZ.

GRUENFELD, G. E. Acutely obstructing carcinoma of the colon. Surg. Clinics N. Am., 1126 (Oct.) 1944.

One in every 3–5 patients with carcinoma of the large bowel (rectum and rectosigmoid excluded) suffers an attack of acute obstruction. In most instances, some previous symptoms of intestinal stenosis are present. Contributory factors are inflammatory edema, impaction of solidifying feces, kinking of the bowel at the tumor site, or fatigue of the intestinal musculature above the stenosis. Prominent in the symptomatology of the acute obstruction is meteorism, which endangers the viability of the colon. It remains confined to the large bowel provided the ileo-cecal valve remains competent. This is of considerable diagnostic aid, roentgenographically, as well as the examination of stomach contents for the presence of fecal matter.

Decompression is urgent and should be effected preferably by a lateral cecostomy with very little bowel manipulation. At a later date resection of the malignancy and anastomosis can be accomplished, and finally closure of the colostomy. The curability rate need not be influenced by the obstruction, providing the decompression alone is done at the first stage, and intelligent surgical judgment is utilized.

FRANK G. VAL DEZ.

KILLIAN, S. T., AND INGELFINGER, F. J. Nutritional problems presented by a patient with extensive jejunoileitis. Arch. Int. Med., 73: 466 (June) 1944.

This report presents the results of various therapeutic measures in a case of extensive granulomatous jejunoileitis with pronounced hypoproteinemia. Daily nitrogen balances and other laboratory data were obtained over a period of 42 weeks. The following observations were made: A deficiency in pancreatic amylase complicated the intestinal disease. A positive nitrogen balance was easily established, but the hypoproteinemia and the weight responded only moderately to a high oral intake of proteins and amino acids. Oral administration of a concentrated amylase was followed by a gain in weight and an increase in serum proteins, presumably by an increase in the breakdown and absorption of carbohydrates, which prevented the use of amino acids as a source of bodily energy. The administration of the amylase appeared to inhibit the growth of *Monilia albicans* in the stools.

ALBERT CORNELL.

KAUFMAN, L. R., AND MERSHEIMER, W. L. Sulfonamides in appendicitis. Am. J. Surg., 65: 393 (Sept.) 1944.

The present review of 412 consecutive cases of appendicitis from 3 hospitals was undertaken for a study of results following the introduction of sulfonamides administered by the usual routes, including intraperitoneal instillation. The gross mortality prior to the introduction of sulfonamides was 5.5%, and after their use the rate was reduced to 2.4%.

The average adult dose of either sulfanilamide or sulfathiazole was 12 g.; of this, 9 g. was sprinkled over the local peritoneal space and the balance left in the wound; children received approximately ½ the adult dose. Selected instances require supplemental oral or parenteral sulfonamide administration; the subcutaneous route permits a more constant blood concentration than the intravenous.

Mild toxic manifestations were observed in this series which do not necessarily require cessation or which rapidly disappear when sulfonamide therapy is discontinued. There is apparently little danger of the formation of adhesions from the intraperitoneal application of sulfanilamide, though some observers report them with sulfathiazole powder. With intraperitoneal administration, the incidence of complication and mortality was lower than when only the oral and parenteral routes were employed. Where generalized peritonitis exists, drainage adds considerably to the hazard. Beyond these, the factors of combating shock and dehydration with plasma and saline, proper application of oxygen, improved anesthesia, and gastrointestinal suction decompression have all contributed to the steadily decreasing mortality in appendicitis cases.

MICHAEL W. SHUTKIN.

SPRAGUE, P. H., ANDERSON, W. S., AND AARON, T. H. Long standing fever due to regional ileo-colitis. Am. J. Dig. Dis., 11: 295 (Sept.) 1944.

This is a case report of a 15 year old girl who became ill with polyarticular rheumatism, and fever varying from 100° to 104° daily. For several months there were no other symptoms. Ultimately, the appearance of recurring peri-rectal abscesses led to an X-ray examination of the intestines, and the recognition of an inflammatory lesion of the terminal ileum, cecum, and lower ascending colon. The affected parts of the bowel were removed. The pathological process was said to be that of regional ileo-colitis. The authors conclude that regional ileo-colitis must be considered in a differential diagnosis of indeterminate fevers. Furthermore, they emphasize the possibility that rectal abscesses are a presenting symptom of the disorder.

LEMUEL C. MCGEE.

MCGUIGAN, H. A. The secretion and excretion of bile in relation to constipation. Am. J. Dig. Dis., 11: 282 (Sept.) 1944.

After a review of the literature on researches in bile secretion, the author concludes that bile itself is not a choleretic in the sense of increasing the secretion of bile by the liver. It is pointed out that, on the basis of figures previously reported by investigators, bile products did not increase the bile volume corresponding to the amount given. Administered bile is absorbed in the gastrointestinal tract and "excreted." In this process of excretion, there is a deficit which suggests actually less than normal secretion of bile by the liver during the elimination of the administered bile. The 24 hour volume of bile normally secreted by man is variously estimated to be between 530 cc. and 940 cc. The author accepts the evidence of previous experiments that a decrease in bile flow may cause constipation. Therefore, anything which relieves constipation, whether bile or bile salts, a choleretic or a cathartic, must influence the flow of bile.

LEMUEL C. MCGEE.

SIBLEY, W. L. Meckel's diverticulum—dyspepsia Meckeli from heterotopic gastric mucosa. Arch. Surg., 49: 156 (Sept.) 1944.

The vitello-intestinal duct is a communication between the midgut and the yolk sac of the embryo during the first few weeks of fetal life. Persistence of this duct gives rise to the deformity known as Meckel's diverticulum. It may be present throughout life

and cause no symptoms, but it is always a source of potential danger. The most common pathologic conditions which occur are: (1) inflammatory type; (2) peptic ulcer type, with or without hemorrhage; and (3) intestinal obstruction type, with or without intussusception.

"The treatment of Meckel's diverticulum is surgical and is directed toward relieving the symptoms produced by the diverticulum. If obstruction is present, it must be relieved. If intussusception is present, it must be reduced surgically. If a fistula is present, it must be closed. If the diverticulum is enclosed in a hernia sac, it must be reduced. If recurrent pains are the symptoms, they must be relieved." In addition, all procedures carried out for the relief of symptoms must include excision of the diverticulum. In a number of cases, there is probably a symptom complex resulting from secretion of hydrochloric acid and pepsin by heterotopic gastric mucosa, for which the term dyspepsia Meckeli is suggested.

FRANCIS D. MURPHY.

LIVER AND GALLBLADDER

ANDRIES, G. H., AND KAUMP, D. H. Multiple malignant hemangiomas of the liver. Am. J. Clin. Path., 14: 489 (Sept.) 1944.

The authors report the gross and histologic findings in a 10-day old infant which presented clinically multiple hemangiomas of the skin, an enlarged abdomen with a tumor mass in the right upper quadrant, and a grade II jaundice. The peritoneal cavity contained 200 cc. of free bloody fluid; a reddish purple tumor 1.5 cm. in diameter was present in the retroperitoneal tissues of the right iliac fossa. The liver weighed 395 g. and was dark reddish brown in color, with purplish nodular areas of spongy consistency studding the surface. These areas were confluent in some places, and separated in others by normal appearing liver tissue. On its cut surface, the liver tissue was seen to be largely replaced with these dark reddish spongy areas. Some of these areas had ruptured and caused the hemoperitonium. In the left adrenal there was a similar spongy mass which measured 1.5 cm. in diameter.

Microscopically in the involved organs there were two distinct pictures; one of cavernous form, the other of more compact spongy tissue. The cavernous form presented large dilated spaces, lined with flat endothelial cells, and with connective tissue walls. The more compact areas were made up of larger cells with large vesicular nuclei and vacuolated cytoplasm. Some of the cell groups formed whorls, and presented mitotic figures but no tumor giant cells. The adrenal and the retroperitoneal tumors were of the cavernous type only.

Grouping hemangiomas of the liver into (1) benign angiomas (small and large, single and multiple) and (2) malignant angiomas, one finds a variety of forms and structures. Benign forms are nearly always of the cavernous type; they may be single or multiple, small or large, diffuse or localized, and even pedunculated. Malignant hemangiomas do not differ much in appearance from the benign forms except that there is less tendency to a cavernous and a spongy character. The lining cells show a transition from a flattened to a cuboidal type of cell, which is larger and often occurs in several layers. There is often an alveolar arrangement of the cells. In places they show phagocytic properties, which suggest a reticulo-endothelial origin, and mitotic figures are present. There is less tendency to encapsulation of the cell masses, and in some places a tendency to infiltrate into the surrounding tissues is found. Clinically, there is rapid growth of the liver; anemia and, at times, newly appearing metastatic lesions are recognized, but such cases are not common and usually occur in infancy.

N. W. JONES.

ZINTEL, H. A., RIEGEL, C., PETERS, R., RHOADS, J. E., AND RAVDIN, I. S. Intravenous administration of dextrose in the treatment of patients with disease of the biliary tract. Arch. Surg., 49: 238 (Oct.) 1944.

This study attempted to determine the effectiveness of intravenous administration of dextrose, preoperatively, in an effort to increase liver glycogen in patients with disease of the biliary tract. Biopsy specimens of the liver were taken from 58 patients with disease of the biliary tract. Eighteen of these patients received intravenous dex-

trose preoperatively, and the remaining 40, acting as controls, received no dextrose.

The average glycogen level of the liver of the patients who received intravenous dextrose was 6.1%, or 118% greater than the average glycogen level of the control group. Patients with moderate hepatic damage who received dextrose had an average glycogen level of 5.7%, or 104% more than the level observed in the control group. Thus, it is possible to produce a significant elevation of the glycogen content of the liver in the presence of moderate hepatic damage. However, intravenous administration of dextrose did not significantly lower the fat content of the liver.

FRANCIS D. MURPHY.

GRAEF, I., NEGRIN, J., AND PAGE, I. H. The development of hepatic cirrhosis in dogs after hypophysectomy—its association with unanticipated, coincidental hypothalamic injury. Am. J. Path., 20: 823 (Sept.) 1944.

Early cirrhosis of the liver has been found occasionally in some hypophysectomized dogs. In other similarly operated upon dogs, few or no tissue changes have been noted. The reason underlying this variance of observation is the subject of the above report. The findings in 5 cirrhotic dogs and in 6 non-cirrhotic dogs are given in detail. The dogs had lived from 4½ months to 5 years. Hypophysectomy was performed on the dogs by using a subtemporal approach. The pituitary gland was removed and the infundibular stalk transected by spoon.

The study revealed the fact that in all of the cirrhotic dogs the hypothalamus disclosed defects far greater than those found in the non-cirrhotic animals. The hypothetical explanation is offered that the fatty infiltration and subsequent cirrhosis of the liver are due to an as yet unexplained effect of the hypothalamic injury incident to the operation. Associated visceral and physiologic changes, such as adrenal cortical atrophy, thymic hyperplasia, coat changes, obesity, and diabetes insipidus, could not be related to the presence or absence of hepatic lesions.

N. W. JONES.

GAUSS, H. A review of the rôle of the biliary system in atrophic arthritis. Am. J. Dig. Dis., 11: 271 (Sept.) 1944.

The author believes that the biliary system is related to atrophic arthritis in some patients. The mechanism of this relationship is not obvious. Two probable interrelationships are described: (1) bacterial (gall bladder as a focus of infection), and (2) metabolic (as implied when the arthritic patient develops jaundice and is relieved of symptoms).

Bacteriological studies of the bile and gall bladder in cholecystic disease show pathogenic bacteria in about ⅓ of such cases. Since the etiology of atrophic arthritis is unknown, the relationship of the disease to biliary infection can only be assumed. Likewise, the mechanism of the beneficial effect of jaundice on arthritis is unknown. The implied metabolic relationship awaits further examination by clinical and laboratory studies.

LEMUEL C. MCGEE.

SAHLER, O. D., AND HAMPTON, A. O. The roentgen appearance of common duct stone. Am. J. Roent. Rad. Therapy, 52: 298 (Sept.) 1944.

This report is based on the roentgenologic examination of 12 proven cases of common duct stones. The authors point out the importance of demonstrating common duct opaque stones on the plain roentgenogram. They emphasize that the chief difficulty in diagnosing common duct stones lies in establishing their correct location. The decision as to whether a calculus lies in the common or cystic duct is occasionally difficult. They differentiate the latter locations by the presence of hydrops of the gall bladder and cystic duct stones. In 4 out of 7 cases of proven common duct stones, jaundice was present. The authors describe in detail the differential diagnosis.

MAURICE FELDMAN.

JOHNSON, W., MALSTROM, B. E., AND VOLK, B. W. A clinico-pathologic study of 100 cases of acute and chronic gall-bladder disease. Ann. Int. Med., 21: 431 (Sept.) 1944.

A group of 81 women and 19 men with cholecystic disease are analyzed as to clinical

symptomatology, correlation with microscopic pathologic appearance, and ultimate relief of symptoms. Seventy-one had calculi and 29 did not; 86 were operated during a quiescent interval whereas 14 showed acute symptoms on admission; of the latter 11 showed calculi at operation. In the chronic group 60 out of 86 had calculi. Pathologically, it was noted that microscopic changes were seldom an accurate index of the severity of the symptoms. Lymphocytic infiltration is not thought to be a criterion of chronic cholecystitis. Thickening of the wall is due to sub-serosal edema, fat in the subserous and muscular layers, and fibrosis. As a rule, epithelial changes were minimal.

In follow-up reports of 72 of the 100 patients (65 with chronic cholecystitis and 7 with former acute inflammation) 35 of the 45 who had stones were greatly improved, 4 had only temporary relief, and 6 showed no relief at all. Of the 20 patients of the non-calculous group, 13 reported permanent relief, 3 only temporary relief, and 4 were worse by the operation. Roughly, 75% obtained good results from cholecystectomy, while 25% were unimproved. From a pathologic standpoint, those with removal of definitely pathologic gall bladders presented better clinical results than those in which there were only minimal pathologic changes in the gall bladder.

FRANK G. VAL DEZ.

PANCREAS

EDMUNDSON, H. A., AND BERNE, C. J. Calcium changes in acute pancreatic necrosis. Surg. Gyn. Obs., 79: 240 (Sept.) 1944.

The 3 phases of possible calcium disturbance investigated were: estimations of the total amount of calcium deposited in and around the pancreas, following death from acute pancreatic necrosis; measurments of the total blood calcium on patients with acute pancreatic necrosis; measurements of diffusible and nondiffusible calcium in patients with a lowered total serum calcium.

In 6 fatal cases of acute pancreatic necrosis, from 100 to 1732 mg. of total calcium were present in the areas of fat necrosis. Serum calcium values below 9 mg. per 100 cc. of blood were present in 36 of 50 clinical cases of pancreatic necrosis, some time between the 2nd and 15th day of the disease. The average serum calcium value in the entire series was lowest on the 6th day (8.4 mg.). These values returned to normal slowly in severe cases, lagging behind the clinical course of the disease. Serum calcium values below 7 mg. per 100 cc. of serum indicate a fatal prognosis.

FRANCIS D. MURPHY.

POPPEL, M. H., AND MARSHAK, R. H. The roentgen diagnosis of pancreatic disease. Am. J. Roent. Rad. Therapy, 52: 307 (Sept.) 1944.

The authors arbitrarily divided the roentgen study of the pancreas into 4 groups, as differentiated by: (1) lesions within the pancreas demonstrable on a plain roentgenogram, (2) lesions producing effects on contiguous structures, (3) lesions which produce their effects on structures not intimately related to the pancreas, (4) lesions which are too small to provide any roentgen manifestation. In group one, opaque shadows caused by calculi, foreign bodies, calcification of cysts or other structures, gas abscesses or an unusually dense pancreatic tumor may be demonstrated. Group two comprises tumefactions, enlargement, congenital anomalies, specific and non-specific infections. Group three comprises the condition of meconium ileus, associated pulmonary changes, secondary peritonitis, alteration in the diaphragms. Group 4 comprises cases of diabetes mellitus, hemochromatosis, chronic pancreatitis. Detailed roentgen changes are described for each group. The roentgen findings are based on the anatomical location of the lesion, i.e., in the head of the pancreas, or in the body or tail.

MAURICE FELDMAN.

ANEMIAS

DAVIS, L. J., AND DAVIDSON, L. S. P. Proteolysed liver in the treatment of refractory anaemias. Quart. J. Med., 13: 53 (Apr.–July) 1944.

This report is concerned with the response to oral proteolysed liver in 13 cases of severe anemia, all of which had proved refractory to treatment with injections of liver extracts of known potency. In 5 cases, the morphol-

ogy of the peripheral blood and sternal marrow was macrocytic and megaloblastic, respectively. This was typical of Addisonian pernicious anemia, although only one of the cases conformed fully in other respects to the usual diagnostic criteria for this disease. In all these cases the administration of protcolysed liver resulted in a prompt and vigorous hematopoietic response, and the rapid restoration of the patient to normal health. In 3 other cases, the anemia was also macrocytic but sternal marrow showed "dimorphic" erythropoiesis. Proteolysed liver in these cases was followed by only partial blood regeneration with the survival of the patients in moderate health. The remaining 5 cases of anemia were of the aplastic type with hypocellular normoblastic sternal marrow, and completely failed to respond to proteolysed liver or to any other form of treatment. The significance of these observations is discussed and it is suggested that proteolysed liver contains, in a readily assimilable form, some hematopoietic maturation factor additional to the anti-anemic factor present in fractionated liver extracts.

ALBERT CORNELL.

ASKEY, J. M. The dietary factor in the etiology of pernicious anemia. Ann. Int. Med., 21: 402 (Sept.) 1944.

The essential objective criteria necessary for a diagnosis of typical Addisonian pernicious anemia are (1) permanent histaminc anacidity, (2) permanent reduction of Castle's intrinsic factor, and (3) reduction of the stored anti-pernicious anemia principle in the liver. The anemia, bone marrow changes, and nerve changes are secondary developments. The author found no correlation between the natural distribution of the disease and poor nutrition. It is lowest among people where famine, under-nutrition, and avitaminoses are common; it is found chiefly among those who use a diet high in protein and meat, and are well fed. The macrocytic anemias of the tropics, of pellagra, and of sprue respond to Cohn's liver fraction G, which contains 2 distinct anti-macrocytic anemia principles. Tropical macrocytic anemia does not respond to the Dakin-West fraction.

In experimentally produced pernicious anemia only the hog responds with the essential triad of objective findings to dietary deficiencies (modified Goldberger-Wheeler diet), but this diet in man produces pellagra rather than pernicious anemia. The author feels that climate is of secondary importance to race in the production of pernicious anemia, and hints at the possibility of a true inborn genetic defect as the cause.

FRANK G. VAL DEZ.

ULCER

ZUCKER, T. F., AND BERG, B. N. The time factor in the production of gastric lesions on low calcium diets. Proc. Soc. Exp. Biol. Med., 57: 1 (Oct.) 1944.

The authors have reported previously that gastric lesions develop in rats kept for 4 weeks on a low calcium diet, and that the restoration to normal dietary calcium levels prevents the lesions. There have, however, been indications that time is a distinct factor in determining the end results, and therefore the duration of experiments has been extended. Keeping rats for longer periods of time on low calcium diets accentuated the ulcerative as well as the hyperplastic and hemorrhagic character of the antrum lesions, as against the conditions produced in 4 weeks. It also brought out a generalized tendency to bleeding. The lesions remained superficial however.

H. NECHELES.

STEIGMANN, F., AND BLATT, M. L. Enzyme treated milk in the dietary management of patients with peptic ulcer. Am. J. Dig. Dis., 11: 276 (Sept.) 1944.

The authors report their experience with enzyme treated milk, Enzylac, in the management of 24 patients hospitalized because of peptic ulcer. The milk is prepared by the addition of a proteolytic enzyme, obtained from the pancreas, to fresh milk before pasteurization. Fractional gastric analyses were made during fasting and following test meals. Subjects were selected because of poor tolerance to ordinary milk, as evidenced by complaints of nausea, epigastric distress, and belching following its ingestion. In less than half the patients, higher combined and lower free acidity followed the use

of enzyme treated milk than following the use of ordinary pasteurized milk. The enzyme treated milk gave smaller and softer curds.

LEMUEL C. MCGEE.

PROCTOLOGY

KEYES, E. L. Squamous cell carcinoma of the anus and rectum. Surg. Clinics N. Am., 1151 (Oct.) 1944.

Squamous cell carcinoma occurs more commonly in females in the authors series (34 out of 40), and at an average age of 57 years. The most important factor in the history is rectal bleeding. Clinically, the author divides these cases into "early" (when they are small, less than 4 cm. in diameter, easily accessible, papillary, and freely movable) and "advanced" (when larger, invasive, ulcerative, and fixed). Squamous cell carcinoma metastasizes less often and less widely than does adenocarcinoma.

The treatment is divided into surgery and radiology. The surgical attack consists of preliminary colostomy, followed by perineal excision of the tumor, with or without inguinal lymphatic dissection; the latter has been abandoned by the author in the past 5 years. Radiation is the treatment of choice in the "early" type, since the primary anal squamous cell carcinoma is radio-sensitive. The metastatic lesions are radio-resistant. Radon (when available) is preferred, but radium is used most extensively. In the authors series, 17 were treated by radiation, with 7 survivals beyond a 5 year period (41.2%). In a series of 40 patients treated by either surgery or radiation, 7 out of 40 survived 5 years or more, clinically cancer-free.

FRANK G. VAL DEZ.

WOMACK, N. Adenoma of the rectum. Surg. Clinics N. Am., 1143 (Oct.) 1944.

These lesions occur at all ages, and the problem becomes one of determining whether or not the adenoma is benign or malignant. The microscopic picture of an adenoma of the rectum is one of abnormal growth, in which the cells tend to resemble normal rectal mucosa. They show evidence of increased growth, and more frequently, ulceration and inflammation. The outstanding symptom is painless hemorrhage from the rectum, which may be profuse, but is usually brief. Mucus in the stools is also not uncommon.

Differentiation from malignant lesions by biopsy is frequently misleading unless adequate portions, including the base and underlying muscularis, are obtained. For clinical purposes, the author states, the main difference between benign adenoma and carcinoma of the rectum should be considered one of degree or extent. When it invades the muscularis it is cancer; when it has not so invaded it is an adenoma. As a general rule, macroscopically, when the height of a tumor is greater than the diameter of its base, that tumor is likely to be benign. The author cites 3 cases showing how biopsies are sometimes misleading as to the true nature of an adenoma. The proper treatment when the lesion is benign is complete extirpation. Thus, invasion can be determined microscopically and secondary resection resorted to if indicated.

FRANK G. VAL DEZ.

ALFORD, J. E. Observation of anorectal disease and pilonidal cysts in an army hospital. N. Y. State J. Med., 44: 1997 (Sept.) 1944.

There has been an increase in the proportion of pilonidal cysts treated by army surgeons. One reason is that mechanized warfare has caused more trauma to that region. The jeep is probably the worst offender. The type of surgical procedure is still controversial. Excision and primary closure will give good results, if there is complete hemostasis, and obliteration of dead space. Frequent dressings are discouraged. Buffered crystalline sulfanilamide containing 10% calcium carbonate is suggested for topical application. If primary closure is not feasible, suturing the skin edges to the sacro-coccygeal fascia will obliterate dead space. The majority of cases of hemorrhoids were the combined internal and external types. The treatment of choice is excision. Only 10 days' hospitalization was required in most cases, and patients were permitted to get off bed after 24 hours post-operatively. Post-operative dilatation should be performed at weekly intervals for 5 or 6 weeks after dis-

charge from the hospital, to prevent stricture formation.

Anorectal abscess develops in infected crypts. Abscesses were drained as soon as seen, and if fistulas were present they were excised after the inflammatory reaction had subsided. Only 4 cases of colitis were seen in 2,500 admissions. Two cases were of the non-specific ulcerative types, and the other two were cases of old amebic dysentery. A number of recruits complained of colitis in civil life, but sigmoidoscopic examination showed no pathologic changes in the vast majority. These were regarded as cases of spastic colitis, mucous colitis, or irritable colon.

PHILIP LEVITSKY.

SURGERY

ROSENBLATT, M. S. Gastric lesions high on the lesser curvature. Am. J. Surg., 65: 404 (Sept.) 1944.

Extirpation of either benign or malignant lesions, high on the lesser curvature, often are surgically a difficult technical problem. For certain cases of ulcer or carcinoma in this region (limited in number because of a prohibitive mortality, short survival, postoperative stricture, and even the remote possibility of pernicious anemia) a method of handling is suggested and successfully practiced. The lesion is removed with a double elliptical incision and the adjacent anterior and posterior gastric walls sutured together. This eliminates suture tension and leakage. A posterior gastroenterostomy is then necessary, because the innervation and control of the pylorus are interfered with by the resection of the lesion. Where a high gastric acidity prevails subtotal gastrectomy is the procedure of choice, thus avoiding postoperative stomal ulceration. The primary stage of elliptical excision is illustrated.

MICHAEL W. SHUTKIN.

PHYSIOLOGY: MOTILITY

VAN LIERE, E. J., NORTHUP, D. W., AND STICKNEY, J. C. The effect of anemic anoxia on the motility of the small and large intestine. Am. J. Physiol., 142: 260 (Sept.) 1944.

Following a significant hemorrhage the longitudinal muscles of the colon of the dog may show a decrease in the height or in the number of contractions, a change in tone, or some combination of these factors. A few of the animals studied were highly resistant to the effects of hemorrhage; however, the majority showed a depression in activity of colonic musculature after they had lost a quantity of blood equal to 1.5% of the body weight. Dogs subjected to a hemorrhage equivalent to 3% of the body weight showed that a powdered charcoal-acacia mixture, given by stomach tube, had traversed 74% of the total length of the small intestine at the end of 30 minutes. In contrast, the value for the control group was 55%. No entirely adequate explanation can be offered why anemic anoxia accelerated the propulsive movements of the small intestine.

ARTHUR E. MEYER.

PHYSIOLOGY: ABSORPTION

LEONARDS, J. R., AND FREE, A. H. Intestinal absorption of galactose in the rat as affected by suboptimal intakes of thiamine. J. Nutr., 28: 197 (Sept.) 1944.

The rate of intestinal absorption of galactose was measured in 3 groups of rats which were kept for 70 to 80 days on thiamine intakes of 2 μg., 5 μg., and 10 μg. per day, respectively. The absorption was compared with "paired" control animals receiving 40 μg. of thiamine per day. The rate of absorption of galactose in rats receiving these suboptimal thiamine intakes averaged 85–90% of that of the controls. The methods employed did not indicate any change in the rate of metabolism of galactose as a result of the chronic thiamine deficiency.

ARTHUR E. MEYER.

PERRYMAN, J. H., DE LA MADRID, R., AND BROOKS, S. C. Absence of glucose effect on gastro-intestinal phosphate absorption Science, 2595: 271 (Sept.) 1944.

By the use of tagged (radioactive) ions an attempt was made to determine the relative permeability of the gastro-intestinal wall to phosphate in the presence of glucose, as compared with control solution.

Laboratory rats, without food for 2 days, were fed 0.4 cc. of radioactive phosphate diluted with 4.6 cc. isotonic glucose by stomach tube. Isotonic NaCl or Ringer's was

substituted in the control group. Ten minutes after feeding the animals were killed and autopsied. Stomach and intestinal contents varied to a marked degree, although all animals had been deprived of food for the same period. While no effect of glucose on the uptake of phosphate was found, the experiments lead to the tentative conclusion that if the permeability of the gastro-intestinal tract is affected by glucose, the effect is small, probably within 30%, and unimportant.

FRANCIS D. MURPHY.

METABOLISM AND NUTRITION

FREE, A. H., AND LEONARDS, J. R. Studies on the ingestion of large quantities of protein and amino acids. J. Lab. Clin. Med., 29: 963 (Sept.) 1944.

The changes occurring in blood and urine following ingestion of meat, blood, and amino acids were investigated. The authors served as subjects. The maximum amount of meat was ingested in an 8 hour period. The blood and amino acids taken were equivalent in nitrogen content. Blood and urine samples were collected at intervals. The maximum urea clearance was determined for each interval. A comparable increase in blood amino acid nitrogen and urea nitrogen was obtained with each of the materials ingested—greatest with amino acids and least with meat. The urea nitrogen output in the urine was increased as was the urea clearance. There was no change in the plasma proteins following the intake of amino acids. It appears that the rate of absorption determines the maximum intake of proteins and amino acids. The high osmotic pressure of the amino acid mixture retards the gastric emptying. In an individual with normal kidneys the high urea clearance tends to lower the blood urea level. The azotemia in massive gastro-intestinal hemorrhage suggests functional impairment of the kidneys, probably as a result of diminished blood pressure, but it cannot be used to determine the severity of the hemorrhage. The digestion, absorption, and metabolism of muscle protein do not differ from those of blood protein. Proteins are more readily tolerated by the gastro-intestinal tract than amino acids, which have an irritating effect because of their high osmotic pressure.

PHILIP LEVITSKY.

CAHILL, W. M., SCHROEDER, L. J., AND SMITH, A. H. Digestibility and biologic value of soybean protein in whole soybeans, soybean flour and soybean milk. J. Nutr., 28: 209 (Sept.) 1944.

The average true digestibility in adult human subjects of the protein in cooked whole soybeans, in cooked soybean flour, and in soybean milk was found to be 90.5%, 94.0%, and 89.6%, respectively. The average biological value of soybean protein for maintenance in adult human subjects, as determined by the method of Murlin et al. (in which the protein of whole egg is employed as a standard) was found to be 94.5% for the protein in cooked whole soybeans, 91.7% for that in cooked soyflour, and 95.3% for that in a commercial soybean "milk." Under the conditions of the study, less favorable nitrogen balances were observed when the experimental subjects were fed diets containing soybean products than when they were fed a standard egg diet, owing largely to greater loss of soybean nitrogen in the feces.

ARTHUR E. MEYER.

PHARMACOLOGY

HUFFORD, A. R. Gastroscopic preparation with demerol hydrochloride. Rev. Gastroenterol., 11: 328 (Sept.–Oct.) 1944.

Demerol, a brand of meperidine hydrochloride, has been in use since 1939 for the relief of pain in a variety of medical and surgical diseases—often as a substitute for morphine. Reports on its use have indicated that it is a safe analgesic, which approximates the effectiveness of morphine for the relief of pain. Guttman has cautioned against its use in cases with intracranial lesions.

The efficacy of this drug in the preparation of patients for gastroscopic examination was studied on 38 subjects having a wide range of gastric pathology. The usual local preparation of the oropharynx and upper esophagus was employed, in addition to oral and hypodermic administration of demerol. It was concluded that the best method of administration was hypodermic injection into the

deltoid muscle of 75 to 150 mg., the dose depending upon the size and nervous state of the patient. Adequate effect was obtained 20 minutes after injection, and lasted for 2–4 hours. It is considered a relatively nontoxic drug, and renders gastroscopic examination more efficient and less disturbing to the patient than the usual codein-atropine medication. Further use of the drug is recommended before a final appraisal of its value can be established.

S. A. Overstreet.

Handler, P. Alleviation by raw liver of anorexia produced by sulfadiazinc. Proc. Soc. Exp. Biol. Med., 57: 99 (Oct.) 1944.

It is known that administration of sulfapyridine to dogs with blacktongue does not interfere with alleviation of symptoms by nicotinic acid, but does prevent weight restoration. Raw liver counteracts the sulfapyridine effect. In the present study, it was investigated whether the effects observed with sulfapyridine were due to interference with nicotinic acid metabolism by the drug or to a sulfapyridine induced anorexia. Sulfapyridine produced anorexia and consequent growth failure and weight loss in normal rats and dogs. This was counteracted by raw liver in the diet, but not by dry liver powder or concentrated liver extract. No cogent explanation of these findings can be given at the present time.

H. Necheles.

McGuigan, H. A., Steigmann, F., and Dynewicz, J. M. Evaluation of the laxative effect of some commonly used laxative substances with particular reference to dosage. Am. J. Dig. Dis., 11: 284 (Sept.) 1944.

Normal subjects and constipated patients were used in a comparative study of laxative effects of phenolphthalein, cascara, magnesium sulfate, bran, karaya gum, and a high fruit diet. The preparations were given to groups of 10–50 persons, with the exception of phenolphthalein, which was given to several hundred persons in varying doses. Attention was paid to the weight and consistency of the stools.

The present pharmacopoeial dose of 0.06 g. of phenolphthalein was laxative in less than one-half of the subjects. The authors find that the optimal dose of phenolphthalein is 0.20 g. The pharmacopoeial dose of magnesium sulfate was strongly laxative, but the official U.S.P. dose of aromatic fluid extract of cascara sagrada was inadequate. It is concluded that 4 cc. of fluid extract of cascara sagrada is the optimal dose. Aged patients and children require larger doses of phenolphthalein than does the average adult.

Lemuel C. McGee.

ANATOMY

Hartz, P. H., and van der Sar, A. Proliferative activity in Brunner's glands. Am. J. Path., 20: 931 (Sept.) 1944.

With the object of refuting the conclusions of Robertson's (Arch. Path. 1941, 31, 112–130) study on the Brunner gland of the duodenum in 1000 cases, that "Brunner's glands are apparently non-combatants—the glands become 'spurlos versenkt' ", the authors studied 24 duodena obtained from autopsies performed within one hour of death. In 8 of the cases signs of proliferative activity, i.e. mitotic divisions, were found in the glands. In 4 cases dividing cells were occasionally seen, in 2 they were found easily, in the remaining 2 they occurred in great abundance. In the presence of chronic ulcer of the duodenum, less activity in the gland cells was noted. However, in the presence of acute inflammation, the epithelium of the glands had reacted in the same way as glandular epithelium in other parts of the body. The authors believed that early post-mortem changes will destroy the integrity of these cells in many instances.

N. W. Jones.

MISCELLANEOUS

Nothman, M. M. Effect of ligation of pancreatic ducts on the serum phosphatase. Proc. Soc. Exp. Biol. Med., 57: 15 (Oct.) 1944.

The question, whether the serum phosphatase is influenced by the separation of the pancreatic gland from the duodenum through ligation of its ducts, was studied in 10 dogs. Ligation of the pancreatic ducts resulted in increase of alkaline serum phosphatase in 7 out of 10 animals. The values

reach their peak between the 4th and the 10th day after operation, and remain high between the 10th and 20th day. They are 6 to 8 times higher than the values before operation. Acid serum phosphatase is not influenced by the ligation of the pancreatic ducts.

H. NECHELES.

ELMAN, R. Parenteral fluids and food in gastrointestinal disease. Bull. N. Y. Acad. Med., 20: 220 (Apr.) 1944.

The parenteral administration of food is a relatively new procedure. By intravenous alimentation, one can include all the nutritional elements, and in so doing, spare completely any activity on the part of the gastrointestinal tract. More important, however, is the fact that great advances can be made in the treatment of many gastrointestinal diseases. Adequate parenteral food probably requires but 5 of the 6 nutritional elements. The 6th element, fat, is omitted even though there is considerable evidence that it supplies more than calories in the growing organism. It is also a vehicle for vitamins A and D. Nevertheless, for purposes of maintenance during parenteral nutrition for short periods it is probably not essential. The remaining 5 are: water, electrolytes, calories, protein, and vitamins. The first three of these are commonly introduced in the usual injections of parenteral fluids, i.e., solutions of Ringer's and saline plus glucose. As to vitamins, many of them are available in pure form and can be injected subcutaneously or intravenously. These include vitamin C, thiamin, riboflavin, niacin, and several others.

Nutrition, whether enteral or parenteral, must include consideration of all of the 5 elements listed because it is quite probable that each requires the presence of the others to achieve adequate utilization. Parenteral nutrition is always of limited duration and is used only when the gastrointestinal tract is temporarily out of commission, particularly when an abdominal operation is to be carried out. The parenteral route permits satisfactorily utilization of foods, despite the fact that they do not first reach the liver. Further indicated uses and daily requirements of parenteral food are discussed. Human plasma and amino acid mixtures are the only two methods of introducing protein food parenterally but plasma has certain disadvantages. The advantages of using amino acids in the form of Amigen are emphasized. However, certain untoward reactions must be carefully watched for. The use of parenteral feeding permits rest without starvation in nonsurgical diseases, extends the indications for surgery, facilitates surgical procedures, and minimizes postoperative complications.

ALBERT CORNELL.

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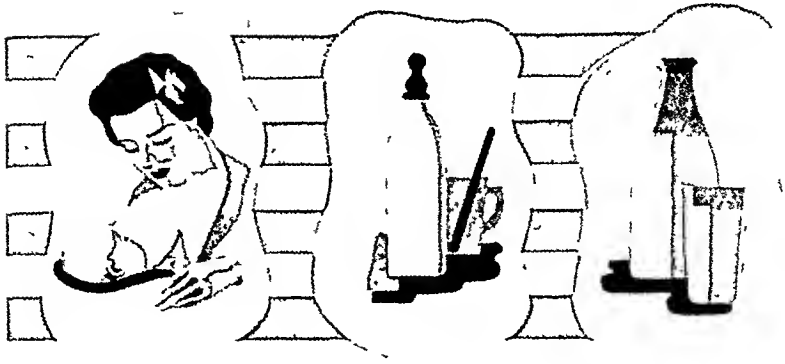

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